The Effects of Acute and Chronic Exercise on Brain Derived Neurotrophic Factor and Cognitive Performance in Mild Cognitive Impairment

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Declaration

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Kate Devenney Date: 10/10/2019

Summary

A growing body of literature suggests that structured exercise interventions may help slow the progression of cognitive decline in people with Mild Cognitive Impairment (MCI), yet little is known about the effects of acute (a single bout of exercise) and chronic exercise on brain derived neurotrophic factor (BDNF) concentration and cognitive performance in this patient population. BDNF, a neurotrophin widely expressed in the brain is upregulated through exercise and believed to enhance neuronal survival, brain plasticity and learning and memory. Exploring the BDNF response to acute and chronic exercise may offer new insights into the underlying mechanism that mediates the exercise-cognitive relationship in a cognitively impaired population. Accordingly, the overarching aim of this thesis was to investigate the effect of acute (varying modality, duration or intensity) and chronic exercise on serum BDNF concentration and cognitive performance in a group of sedentary older adults with MCI.

Work on this study began in September 2015 when I commenced a full-time research post as a PhD candidate on the NeuroExercise study. The NeuroExercise study is a European multi-centre Randomised Controlled Trial (RCT) examining 'The Effects of an Extensive Exercise Programme on the Progression of Mild Cognitive Impairment'. Funding for the NeuroExercise study was awarded by the EU Joint Programme – Neurodegenerative Disease (JPND) Research grant with funding for the Dublin arm of the trial supported by the Health Research Board (HRB). I had responsibility for overseeing study implementation and coordination of the NeuroExercise study at the Dublin site which ran for a 32-month duration. Duties included ethics applications, participant screening and recruitment, study assessments, implementation of the 12-month NeuroExercise exercise protocol, data management and liaising with local referring sites and international partners. The NeuroExercise study recruited from the German Sports University in Cologne, Radboud University Medical Centre in Nijmegen, the Netherlands and Trinity College Dublin. In this study, participants (n=62 at the Dublin site) were randomised to either a yearlong aerobic exercise intervention, balance and toning (non-aerobic) exercise intervention or control group. The primary outcome was change in cognitive performance as measured by a neuropsychological test battery.

Prior to designing the PhD studies contained within this thesis, a systematic review was conducted to highlight existing gaps in the literature relating to exercise in MCI. Following

this, specific research questions and a study protocol was formulated. Participants with MCI, recruited to participate in the NeuroExercise study also consented to participate in all studies within this PhD thesis. Studies I - III were designed to address gaps within the literature and answer specific research questions around acute exercise, BDNF and cognitive performance in an MCI cohort. Results in Study I demonstrated that a short bout of high intensity exercise increased serum BDNF (sBDNF) concentration compared to a resting control condition. While high intensity interventions were feasible in this patient group, the increase in sBDNF did not result in improvements in cognitive performance. Study II and III examined the effect of manipulating acute exercise variables (intensity, duration and mode) on sBDNF concentration and cognitive performance. Results found no difference between varying aerobic exercise conditions (short bout high intensity versus longer bout moderate intensity) or between two distinct exercise modalities (aerobic versus balance and toning) on study outcomes.

Study IV and V examined the effects of purposeful structured exercise training. Study IV investigated whether 12 weeks of exercise training: 1) altered basal sBDNF concentration and cognitive performance and 2) augmented the acute exercise BDNF and cognitive response. Results revealed significant increases in basal sBDNF concentration following 6 weeks of supervised aerobic or balance and toning exercise training. Finally, Study V provided insights into the relationship between sBDNF concentration, episodic memory and cardiorespiratory fitness following participation in a 1-year exercise intervention. Results showed a 1-year exercise intervention with poor levels of adherence did not impact BDNF or cognition.

Overall, results indicate that acute and chronic exercise paradigms can alter the BDNF profile in MCI cohorts. Information gained from these studies will add to the growing body of literature around the effect of acute and chronic exercise, and will help inform exercise prescription and current practice for optimising brain health in a cognitively impaired population.

Acknowledgement

First and foremost to my supervisors. Making the move from a clinical physiotherapy post to a research position was a daunting process and would not have been possible without your support and guidance. To Professor Brian Lawlor, thank you for welcoming me to the memory clinic team in St. James's Hospital and for your leadership and support over the last few years. Your advocacy work, and tireless pursuit in research will leave a lasting impact on the lives of people living with dementia in Ireland. To Dr Emer Guinan, who was always a voice of reason, a wealth of wisdom and provided sound advice throughout. Thank you for your patience - no problem was ever too big or too small and you continually gave selflessly of your time, energy and expertise. I wish to thank you unreservedly for your unwavering support and endless reading of chapters (even when you were supposed to be off the clock!). I couldn't have done this without you.

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I would like to dedicate this to all the strong women who have been influential in my life, especially my grandmothers Kitty and Betty.

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List of Abbreviations

ACSM	American College of Sports Medicine
AD	Alzheimer’s disease
ADAS-cog	Alzheimer's Disease Assessment Scale-cognitive subscale
aMCI	Amnestic Mild Cognitive Impairment
AAN	American Academy of Neurology
ANOVA	Analysis of Variance
ApoE	Apolipoprotein E
AT	Aerobic Exercise Training
AVLT	Auditory Verbal Learning Test
BAT	Balance and Toning Exercise
BBB	Blood Brain Barrier
BDNF	Brain Derived Neurotrophic Factor
BP	Blood Pressure
CANTAB	Cambridge Neuropsychological Test Automated Batteries
CE	Commission Errors
CFQ	Cognitive Failures Questionnaire
CI	Confidence Interval
CPET	Cardiopulmonary Exercise Testing
CR	Cardiorespiratory
CRF	Clinical Research Facility
CRT	Choice Reaction Time
DSST	Digit Symbol Substitution Test
ECG	Electrocardiogram
EDTA	Ethylenediamine Tetraacetic Acid
EG	Emer Guinan
ES	Effect Size
FITT	Frequency Intensity Time Type
HRB	Health Research Board
HR	Heart Rate
HRmax	Heart Rate Max
HRR	Heart Rate Reserve
ICCs	Intraclass correlation coefficients
IGF-1	Insulin Growth Factor-1
IQR	Interquartile Range

KD	Kate Devenney
M	Mean
Md	Median
MCI	Mild Cognitive Impairment
MDC	Minimal Detectable Change
METs	Metabolic Equivalent
MMSE	Mini–Mental State Examination
MoCA	Montreal Cognitive Assessment
MRI	Magnetic Resonance Imaging
PA	Physical Activity
PAL	Paired Associate Learning
PALTEA	Paired Associate Learning Total Errors Adjusted
PPMCC	Pearson Product Moment Correlation Coefficients
RAVLT	Rey Auditory Verbal Learning Test
RCT	Randomised Controlled Trial
REC	Research and Ethics Committee
ROCF	Rey–Osterrieth Complex Figure
RPE	Rate of Perceived Exertion
RT	Reaction Time
SART	Sustained Attention to Response Task
sBDNF	Serum Brain Derived Neurotrophic Factor
SCWT	Stroop Colour Word Task
SDMT	Symbol Digit Modalities Test
SJH	St. James's Hospital
SNST	Stroop Neuropsychological Screening Test
SD	Standard Deviation
SRT	Simple Reaction Time
TBI	Traumatic Brain Injury
TMT	Trail Making Test
VO_2max	Maximal Oxygen Uptake
VO_2peak	Peak Oxygen Uptake
WAIS	Wechsler Adult Intelligence Scale
WMS	Wechsler Memory Scale

List of Appendices

Dissemination of Research

Bursary award:

- Recipient of the 2017 Irish Society of Chartered Physiotherapists Glennon AIG Bursary (€2500) for my project entitled "The effects of acute exercise on cognitive performance and brain-derived neurotrophic factor (BDNF) in individuals with Mild Cognitive Impairment (MCI)

Published papers:

- **Devenney, K.E.,** Sanders, M.L., Lawlor, B., Rikkert, M.G.O. and Schneider, S., 2017. The effects of an extensive exercise programme on the progression of Mild Cognitive Impairment (MCI): study protocol for a randomised controlled trial. BMC geriatrics, 17(1), p.75. (Appendix I)

- Sanders, M.L., Stuckenschneider, T., **Devenney, K.E**., Lawlor, B., Schneider, S., Rikkert, O., Marcel, G.M. and NeuroExercise Study Group, 2018. Real World Recruiting of Older Subjects with Mild Cognitive Impairment for Exercise Trials: Community Readiness is Pivotal. Journal of Alzheimer's Disease, 62(2), pp.579-581. (Appendix II)

Papers under review:

- High intensity acute aerobic exercise effects Brain Derived Neurotrophic Factor (BDNF) in Mild Cognitive Impairment (MCI): a randomised controlled study. 2018. Devenney, K.E, Guinan, E.M., Mota, B.C, Kelly, A.M., Olde Rikkert, M.G.M., Schneider S., and Lawlor, B.

Currently submitted for British Journal of Sports Medicine for review

Conference oral presentations:

Irish Gerontological Society - Postgraduate Study Day in Ageing Research - Friday 27th April 2018, St Vincent's Hospital, Dublin

- The effects of a short bout of high intensity aerobic exercise on serum brain derived neurotrophic factor (BDNF) concentration and cognitive performance in individuals with Mild Cognitive Impairment (MCI). Kate Devenney, Brian Lawlor, Aine Kelly, Bibiana Mota (Dublin/Ireland), Cathal Walsh (Limerick/Ireland),

Marcel Olde Rikkert (Nijmegen/Netherlands), Stefan Schneider (Cologne/Germany), Emer Guinan (Dublin/Ireland)

Health Across Lifespan (HAL) - International conference on healthiness and fitness across the lifespan. September 12–15, 2018, Otto von Guericke University Magdeburg, Germany. Winner of 3rd prize for Best Oral Presentation / Young Researcher Award of HAL 2018. Presentation title as above.

Public and patient dissemination:

- Sharing of recruitment experiences with CANDI research investigators meeting April 4th 2018, Trinity College Dublin
- Public talk on 'Exercise and Brain Health' at the Alzheimer's Café Glasnevin April 2018
- Education session 'Exercise and Brain Health' given to the cognitive rehabilitation MCI group at the memory clinic, St. James's Hospital
- Key note speaker at the Physiotherapy Department Research Presentations, St. James's Hospital July 2018
- Opinion piece entitled 'Exercise and Alzheimer's disease: Current Perspectives' was published in the February 2017 edition of Forum, the journal of the Irish College of General Practitioners (Appendix III)

1 Chapter 1: Introduction

1.1 Mild Cognitive Impairment

Mild Cognitive Impairment (MCI) is a clinical syndrome with a continuum of symptoms and is regarded as an intermediate stage between the cognitive change associated with normal aging and dementia (Petersen, 2004). MCI is marked by either focal or multifocal cognitive impairment, with minimal impairment of instrumental activities of daily living, which is a defining threshold for a dementia diagnosis (Dubois et al., 2010). MCI can be broadly classified into two subtypes: 1) amnestic MCI is a syndrome in which memory dysfunction is the predominant cognitive impairment and 2) non-amnestic MCI in which the primary cognitive impairment is established within another cognitive domain (e.g., language, visuospatial, executive) (Gauthier et al., 2006, Petersen and Negash, 2008).

Alzheimer's disease (AD) is the leading cause of dementia in the aging population, affecting more than 30 million people worldwide (Barnes and Yaffe, 2011). Some forms of MCI are considered a clinical prodrome to AD and other dementias and approximately 15-20% of people over the age of 65 are affected by MCI (Roberts and Knopman, 2013). The Irish Longitudinal Study on Ageing (TILDA), a large population-based study (n=8504) identified a 9% incidence of MCI in community dwelling adults aged 50 and over in Ireland (Kearney et al., 2011). Numerous epidemiological studies have documented an accelerated rate of progression to AD and dementia in MCI subjects, with 10-15% of people with MCI progressing to dementia per year (Farias et al., 2009, Petersen et al., 1999), classifying them as a high-risk group (Figure 1:1). Individuals with aMCI, with or without deficits in other cognitive domains are the most likely MCI subtype to convert to AD (Petersen et al., 2001, Bäckman et al., 2004).

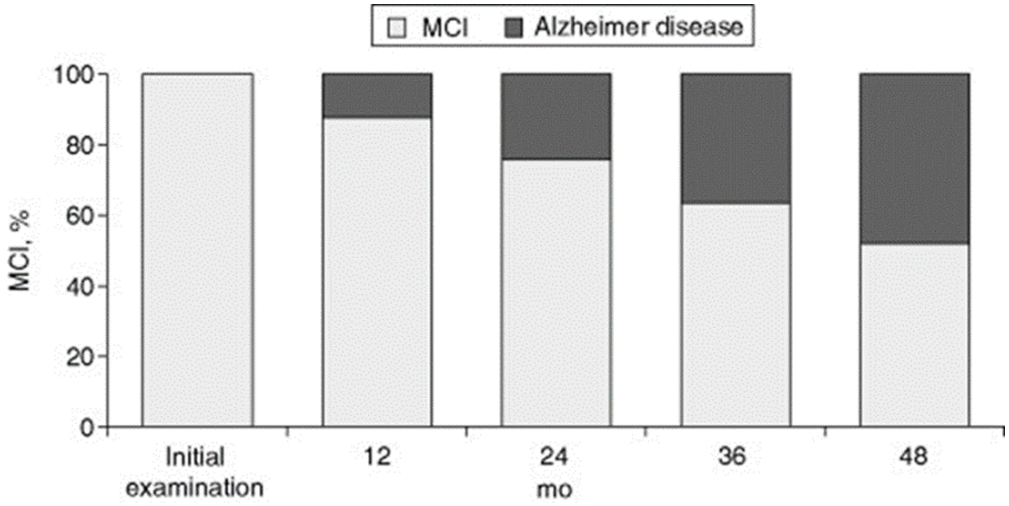

Figure 1:1 Annual rates of conversion from mild cognitive impairment (MCI) to dementia over 48 months (Petersen et al., 1999)

As our ageing population increases, the number of people living with dementia in Ireland is expected to rise to over 130,000 by 2041 (Pierce et al., 2014), which is consistent with the rising occurrence of dementia worldwide (Ferri et al., 2005). The estimated annual cost of dementia care in Ireland in 2010 was over €1.69 billion (Cahill et al., 2012). At the 2013 summit on dementia convened by G8 in London, a range of initiatives were announced in which leading nations made commitments to actively work towards a cure or disease modifying treatment for dementia by 2025 (Dementia, 2014). With the ongoing difficulties' in establishing new disease modifying drugs, research studies into non-pharmacological strategies to prevent dementia, and to optimise cognitive function in older people, particularly individuals at risk of developing dementia, have been increasing in number (Pieramico et al., 2014).

1.2 The aging brain

As people age, there is a decline in a number of physiological functions including reduced immune function, loss of muscle mass and strength, a decrease in bone mineral density and an increase in fat mass (Lamberts et al., 1997, Rudman and Rao, 1992). Furthermore, increases in blood pressure and inflammatory load are also known to occur during the aging process, with both independently linked to risk for dementia and cognitive decline (Qiu et al., 2005, Singh and Newman, 2011, Yaffe et al., 2004).

In addition to this, changes in the medial temporal lobe and prefrontal cortex can lead to a shift in several mechanisms that support numerous cognitive processes (processing speed, memory and executive control processes such as inhibition, planning and

working memory), and appear especially sensitive to age-related change (Rypma and D'Esposito, 2000, Salthouse, 1996, Kausler, 1994, De Luca et al., 2003, Singh-Manoux et al., 2012, Burke and Barnes, 2006, Glisky, 2007). The susceptibility to learning and memory impairments is generally attributed to a decrease in neuronal plasticity of the cortex and hippocampus, which is considered vulnerable to the aging process and has been directly related to the decline of cognitive performance (Barrientos et al., 2015, Morrison and Baxter, 2012).

In aMCI, memory impairments (recognition memory and free recall) arise early in the clinical presentation because they rely heavily on areas affected in the early stages of Alzheimer's neuropathology i.e. the spread of neurofibrillary tangles and neuropil threads in the medial temporal lobe, initially in the transentorhinal cortex and then in the entorhinal cortex and hippocampus (Braak and Braak, 1991, Petersen et al., 2006). Longitudinal Magnetic Resonance Imaging studies have reported significantly greater grey matter loss in the hippocampal area, inferior and middle temporal gyrus, posterior cingulate, and precuneus in those with MCI who transition to AD (Chetelat et al., 2005, Fennema-Notestine et al., 2009). However, an autopsy study found those clinically diagnosed with MCI (including aMCI) presented as pathologically heterogeneous, with a number of people exhibiting mixed pathologies (Schneider et al., 2009).

1.3 Protective factors against cognitive decline

Strong evidence from large population-based studies have facilitated a better understanding of lifestyle factors that are protective against cognitive decline, AD and dementia. Modifiable risk factors include engagement in cognitively stimulating activity (Hughes et al., 2010, Pillai et al., 2011, Baumgart et al., 2015); social engagement (Ellwardt et al., 2015, Holt-Lunstad et al., 2010, Fratiglioni et al., 2004); level of education (Clouston et al., 2012, Tervo et al., 2004, Sattler et al., 2012); self-efficacy (Davis et al., 2012); physical activity (Colcombe and Kramer, 2003b, Beydoun et al., 2014, Sattler et al., 2011, Fratiglioni et al., 2004); and cardiovascular risk factors (diabetes, obesity, smoking, and hypertension) (Tervo et al., 2004, Baumgart et al., 2015). Fratiglioni et al. (2004) suggest that these lifestyle components, encompassing a combination of social, mental, and physical health share common pathways and may converge within the major aetiological hypotheses for AD and dementia. However, a genetic predisposition and accumulation of exposure to risk factors can only be partially mitigated by modifiable protective factors such as increasing physical activity (Fratiglioni et al., 2004) (Figure 1:2).

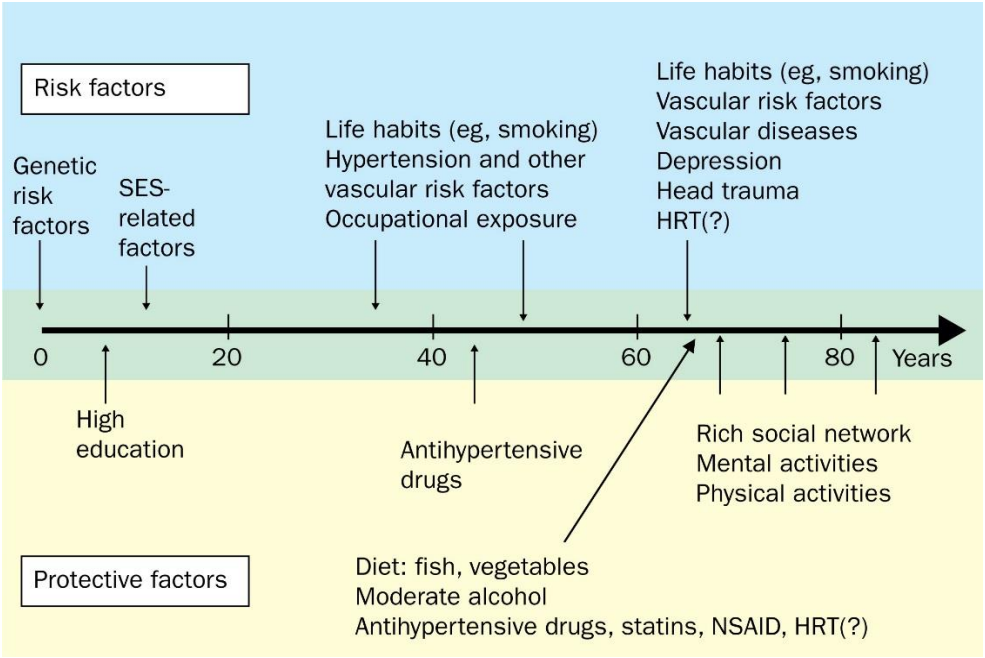

Figure 1:2 The timeline of risk factors and protective factors for dementia. SES: Socio-Economic Status. NSAID: Non-Steroidal Anti-Inflammatory Drug. HRT: Hormone Replacement Therapy (Fratiglioni et al., 2004)

Physical inactivity has been identified as the strongest modifiable independent risk factor, accounting for up to 12.7% of the risk of AD (Barnes and Yaffe, 2011, Norton et al., 2014). In a recent Lancet report, Livingston et al. (2017) estimate that approximately 35% of all dementia cases worldwide could be prevented by targeting nine modifiable risk factors, amenable to intervention. Using population attributable fractions, the nine identified risk factors include early life education; midlife hypertension, obesity, hearing loss, old-age smoking, depression, physical inactivity, diabetes, and social isolation. Within this report, it was projected that over 3% of dementia cases could be prevented by increasing physical activity alone. However, as evident (Figure 1:3), exercise plays a key central role across several the brain mechanisms involved in preventing dementia including; reduced brain inflammation, vascular, neurotoxic and oxidative stress in addition to increasing cognitive reserve (Livingston et al., 2017).

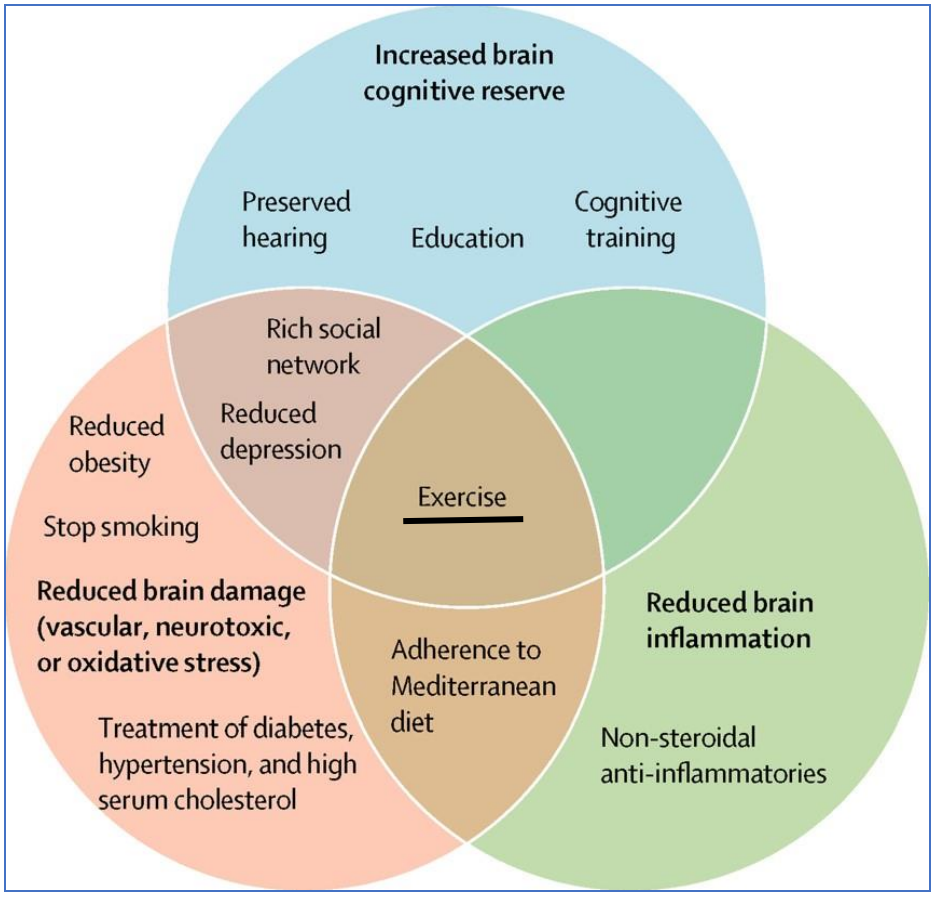

Figure 1:3 Potential brain mechanisms for preventive strategies in dementia (Livingston et al., 2017)

It must also be noted that a number of non-modifiable risk factors for dementia and cognitive decline have also been identified which include higher age (Tervo et al., 2004); female sex (Fratiglioni et al., 2000), a genetic predisposition (apolipoprotein E (ApoE) E4 allele) (Tervo et al., 2004); and a lower socio-economic status (Sattler et al., 2012).

1.4 Cognitive function, physical activity and exercise

Physical Activity (PA) is defined as any bodily movement produced by skeletal muscles that results in energy expenditure. Exercise is considered a subset of PA and involves planned, structured, and repetitive movement that has an intermediate objective of improving or maintaining physical or cardiorespiratory (CR) fitness (Caspersen et al., 1985). These definitions are offered as an interpretational framework for discussing PA, exercise, and cognitive function.

Within a sedentary society, a lack of physical exercise is known to provoke cardiovascular, metabolic and metastatic diseases (Allison et al., 1999, Powell and Blair,

1994). However, the emergence of PA as a mediator of cognitive function is of particular interest due to its modifiable nature (Kramer et al., 2006). Converging evidence from both animal and human studies, suggest that a physically active lifestyle acts as a promoter of brain health mediating neural homeostasis via neuroprotective and neurorestorative mechanisms, thereby counteracting brain ageing and preserving cognitive function (Hill et al., 1993, Rowe and Kahn, 1997, Cotman and Berchtold, 2002, Colcombe and Kramer, 2003b, Palleschi et al., 1996). In older adults, associations have been demonstrated between PA and global cognition (Colcombe and Kramer, 2003b), executive function (Angevaren et al., 2008b, Erickson and Kramer, 2009b) and memory (Floel et al., 2010). Historically a relatively consistent relationship between higher PA levels and a reduced risk of developing dementia has been established (Buchman et al., 2012, Sattler et al., 2011, Yaffe et al., 2001, Cotman and Berchtold, 2002). However, a small number of observational studies failed to report a positive relationship between PA and cognition or dementia (Sturman et al., 2005, Wilson et al., 2002, Yamada et al., 2003), and recent epidemiological data has not replicated the positive associations reported previously (Brasure et al., 2018, Sabia et al., 2017). Furthermore, a Cochrane review found that PA interventions of varying intensity, duration or frequency, including those that successfully improved CR fitness, presented no cognitive benefit to cognitively healthy older adults (Angevaren et al., 2015).

One issue with PA epidemiological study designs, is that results may distort observational associations and impede the distinction between correlation and causation. Another criticism of a number of the observational PA studies is the broad use of only self-report activity without objective measurements of PA, which may be prone to social desirability biases with artificially inflated rates of participation (Erickson et al., 2012b). Clear definition between the various modalities and quantities of PA behaviour is necessary to clarify the relationship between PA and cognitive function including the distinction between aerobic and nonaerobic physical activities (Barnes et al., 2003).

A recent update to the American Academy of Neurology practice guideline on MCI now includes a recommendation for regular exercise as part of overall disease management (Petersen et al., 2018). Specific to MCI, cross-sectional studies have established that moderate PA during midlife (50-65 years), is associated with a lower risk of having MCI in later life (0.61 95% Confidence Interval (CI), 0.43-0.88; p=.008), with late-life participation in moderate exercise also associated with lower risk for MCI (0.68 95% CI, 0.49-0.93; p=.02) (Geda et al., 2010). A meta-analysis of randomised controlled trials

(RCTs) by Heyn et al. (2004) reported that PA (defined as any exercise program or form of rehabilitative exercises, physical activity, fitness, or recreational therapy) increased physical fitness and improved cognitive function in adults with cognitive impairment, with a large effect size (Effect Size (ES)=0.57). The most recent meta-analytic review by Ströhle et al. (2015) found that exercise interventions had a large pooled ES in AD (SMCR=0.83, 95% CI 0.59 to 1.07) and small ES in MCI (SMCR=0.20, 95% CI 0.11 to 0.28), suggesting that physical exercise has larger effects on cognition than drug therapy.

In recent years, a broad range of exercise intervention studies have demonstrated cognitive benefits can be achieved with varying exercise modalities in populations with MCI (Baker et al., 2010a, Nagamatsu et al., 2013b, Nascimento et al., 2014a, Lautenschlager et al., 2008). Aerobic exercise in particular has received the most attention within the literature and interventional studies have reported significant improvements in global cognitive scores (Mini-Mental State Examination (MMSE) scores: 0.98, 95% CI 0.5 to 1.45, $p<0.0001$; Montreal Cognitive Assessment (MoCA) scores: 2.7, 95% CI 1.11 to 4.29, $p=0.0009$) with a weak but significant effect on memory in older adults with (immediately recall: 0.29, 95% CI 0.13 to 0.46, $p=0.0005$; delay recall: 0.22, 95% CI 0.09 to 0.34, $p=0.0005$) (Zheng et al., 2016), and small positive effects for tasks measuring verbal fluency (ES=0.17) in people with MCI (Gates et al., 2013). To further examine the effect of structured aerobic exercise interventions on cognitive performance in MCI, a systematic review of this literature will be presented in Chapter 3.

1.5 The impact of acute and chronic exercise on cognitive function

Both acute and chronic exercise have been proposed and explored as interventions that may augment cognitive function and slow cognitive decline (Ahlskog et al., 2011). The acute exercise response and the chronic adaptations to exercise training cannot be viewed in isolation, because frequent repetition of isolated sessions with transient changes produces permanent functional and structural adaptations. However, acute and chronic exercise represent two theoretical and functionally distinct yet complementary strategies that may augment cognitive function (Roig et al., 2013). Chronic exercise protocols involve repetitive bouts of exercise which occur over an extended time period lasting from weeks to years. Cognitive changes accrued as a result of chronic exercise are assumed to reflect positive structural adaptations and durable changes such as angiogenesis (Swain et al., 2003), synaptogenesis (Dietrich et al., 2008) or neurogenesis

(van Praag et al., 1999a) in areas of the brain that support cognitive process. Changes in cardiovascular health, production of Brain Derived Neurotrophic Factor (BDNF), insulin sensitivity, stress, and inflammation have all been explored as potential mechanisms underlying the exercise-cognitive relationship (Kennedy et al., 2017).

Acute exercise refers to the practice of a single bout of exercise lasting from a few seconds to perhaps several hours (Dietrich and Audiffren, 2011). Behavioural and psychological changes in cognitive performance induced as a result of acute exercise paradigms are assumed to be transient in nature, generally occurring at some point during or quite rapidly after the beginning of exercise (seconds to minutes) and disappearing relatively quickly following exercise cessation (minutes to hours). Rationale for using acute exercise to improve memory is attributed to biological and psychological theories (McMorris and Hale, 2012). Psychological theories propose that a single bout of exercise optimises the level of arousal and therefore facilitates cognitive processing (Audiffren et al., 2008) and memory consolidation (Berlau and McGaugh, 2006). Biological mechanisms implicated in these processes include increased cerebral blood flow (Erickson et al., 2011); reduced neuroinflammation (Parachikova et al., 2008); increased circulation of neurotrophins (Ferris et al., 2007) and neurotransmitters, which may augment cognition (Brisswalter et al., 2002).

1.6 Brain Derived Neurotrophic Factor

Brain-derived neurotrophic factor (BDNF) is a basic protein and a member of the neurotrophin family of growth factors that plays an important role in neuronal regulation, survival, repair, differentiation and plasticity by activating the receptor tyrosine kinase TrkB and p75 low-affinity neurotrophin receptor (Huang and Reichardt, 2001, Poo, 2001, McAllister et al., 1999, Yang et al., 2014, Egan et al., 2003). Among the neurotrophin family, BDNF has emerged as crucial mediator of neuronal plasticity, since it is highly concentrated in brain regions particularly relevant for plasticity and responsible for higher cognition (the hippocampus and cortex), but also because it plays a vital role in learning and memory and has demonstrated activity-dependent regulation of expression and secretion (Bramham and Messaoudi, 2005, Poo, 2001, Tyler et al., 2002, Cowansage et al., 2010, Bekinschtein et al., 2014).

BDNF has demonstrated the ability to transit the blood–brain barrier (BBB) in both directions, with peripheral levels presenting a strong correlation with the central levels (Pan et al., 1998, Poduslo and Curran, 1996, Seifert et al., 2009). Since BDNF may cross

the BBB in both directions, it has been suggested that a substantial proportion of the circulating BDNF may originate from neurons and glial cells within the central nervous system (Pan et al., 1998). In the peripheral system, BDNF is stored in platelets and released during clotting processes, which leads to concentrations of serum BDNF being approximately 200-fold higher relative to the concentration of plasma BDNF (Fujimura et al., 2002). However, BDNF also has the capacity to be produced within tissues in the periphery, leading some authors to question whether BDNF changes in serum levels are the result from changes in central or peripheral BDNF processes (Erickson et al., 2012a, Murer et al., 2001). Furthermore, it should be noted that a large degree of variability and individual differences in BDNF are not unexpected and a number of influencing factors have been identified including; age, gender, weight status, diurnal fluctuations, diet and disorders of the metabolic or immunological systems (Lommatzsch et al., 2005, Szuhany et al., 2015).

1.6.1 BDNF in aging, MCI and AD

Converging preclinical and human studies suggest that BDNF may influence late-life cognitive impairment (Diniz and Teixeira, 2011, Forlenza et al., 2015). Research has shown that BDNF concentrations decrease with progressive age-related neuronal loss (Lommatzsch et al., 2005, Ziegenhorn et al., 2007, Webster et al., 2006), with some studies demonstrating a positive association between BDNF concentration and cognitive performance in healthy older adults (Gunstad et al., 2008, Komulainen et al., 2008), although this is not consistent across studies. Correlational evidence has shown that peripheral measures of BDNF are associated with hippocampal volume and spatial memory in older adult cohorts (Erickson et al., 2010). Similarly, attenuated loss of BDNF has been reported in MCI cohorts compared to elderly controls and this has shown to correlate with loss of cognitive function, especially in tests of episodic memory (Forlenza et al., 2015, Peng et al., 2005, Yu et al., 2008). A large (n=4463) cross-sectional observational study of community dwelling older adults, found low serum BDNF was associated with lower cognitive test scores on story memory and digit symbol substitution tasks but only marginally associated with the presence of MCI (Odds Ratio (OR), 95% Confidence Interval (CI): 1.41, 1.00-1.99) (Shimada et al., 2014). A random-effects meta-analysis showed that patients with AD had significantly decreased baseline peripheral blood levels of BDNF compared with healthy control subjects (24 studies, Hedges' g=−0.339, 95% CI =−0.572 to −0.106, P=0.004) (Qin et al., 2017). Furthermore, subjects with MCI showed a trend for decreased BDNF levels compared with healthy control subjects (14 studies, Hedges' g=−0.201, 95% CI=−0.413 to 0.010, P=0.062) but

no differences were found between AD and MCI subjects in BDNF levels (11 studies, Hedges' g=0.058, 95% CI=−0.120 to 0.236, P=0.522) (Qin et al., 2017). While a number of studies have found peripheral BDNF to be significantly reduced in MCI and AD patients compared to healthy controls (Forlenza et al., 2015, Lee et al., 2009), increased peripheral BDNF has been reported among a number of other studies (Angelucci et al., 2010, Laske et al., 2006). In addition to MCI, decreased peripheral levels of BDNF have been observed in a number of psychiatric and neurodegenerative disorders including anxiety, depression and AD and dementia (Phillips et al., 1991, Yasutake et al., 2006, Brunoni et al., 2008, Chen et al., 2006). However, consensus opinion on the role BDNF plays in the neuropathology of these disease processes, including AD and MCI is equivocal.

Although the above-mentioned studies comparing diagnosed MCI and AD patients with healthy controls failed to find consistent differences in serum BDNF levels between groups, Laske et al. (2006) suggest that peripheral levels of BDNF may increase in the early stages of the disease as a compensatory repair mechanism and then decrease according to the severity of the neurodegeneration and Aβ amyloid accumulation. Another plausible explanation for inconsistent results regarding the levels of BDNF for individuals with MCI is the differences in the methodology used to classify MCI patients and the inclusion different of different MCI subgroups (Borba, 2012).

1.6.2 BDNF response to exercise

Physical exercise is capable of inducing a cascade of molecular and cellular processes which promote angiogenesis, neurogenesis and brain synaptogenesis (Deslandes et al., 2009, Eggermont et al., 2006, Lista and Sorrentino, 2010). The neurobiological mechanisms responsible for the beneficial effects of physical exercise on cognition include, the increase of brain blood flow in several cortical and subcortical areas that results in an increase in the synthesis and use of neurotransmitters (Pereira et al., 2007, Burdette et al., 2010), a decrease in the formation of the beta amyloid protein (Adlard et al., 2005), and an increase in the synthesis and release of BDNF (Coelho et al., 2014). Among the large body of animal research, a characteristic finding is the exercise-induced increase in BDNF in the hippocampus, an area involved in learning and memory formation (Vaynman et al., 2003, Neeper et al., 1995). Exercise-induced BDNF activity has demonstrated the ability to reduce the threshold for successful encoding and memory (Intlekofer and Cotman, 2013) and has been hypothesised to place the brain in a state of readiness for plasticity (Cotman et al., 2007).

A recent meta-analysis found that exercise interventions led to higher resting concentrations of peripheral BDNF in healthy adult populations (0.39, 95% CI: 0.17–0.60, p < 0.001), with results indicating a significant effect in aerobic (0.66, 95% CI: 0.33–0.99, p < 0.001) but not resistance training (0.07, 95% CI: -0.15–0.30, p = 0.52) (Dinoff et al., 2016). Similarly, a single session of exercise has been shown to increase concentrations of peripheral BDNF in an intensity-dependent and transient nature (Schmidt-Kassow et al., 2014, Ferris et al., 2007, Tang et al., 2008, Saucedo Marquez et al., 2015, Schmolesky et al., 2013, Knaepen et al., 2010). Szuhany et al. (2015) reported pre-post exercise change in BDNF levels across a single exercise session reflected a moderate ES (Hedges' g = 0.46, SE = 0.08, 95% CI = 0.30–0.63, z = 5.54, p < 0.001). The most recent meta-analysis examining the effect of acute exercise on peripheral blood BDNF concentration in healthy adults also found a significant increase after a single session of exercise (SMD = 0.59, 95% CI: 0.46–0.72, P < 0.001), with longer duration of exercise associated with greater increases in BDNF (Dinoff et al., 2017).

Conclusion of both reviews are in agreement with earlier research that stated the magnitude of change in response to acute aerobic exercise is intensity and duration dependent. Schmidt-Kassow et al. (2014) showed that BDNF levels gradually increased, reaching maximal levels after 20 min of exercise and returned to baseline values after 10 minutes of recovery. Several studies have demonstrated that short episodes of high intensity exercise result in increased serum levels of BDNF in humans with serum concentration appearing to return to pre-exercise baseline levels within 30–50 minutes following cessation of activity (Ferris et al., 2007, Tang et al., 2008). A review by Knaepen et al. (2010) described a dose-response relationship between acute exercise and peripheral BDNF concentrations, with high intensity and graded exercise tests eliciting the greatest exercise-induced increases in peripheral BDNF concentration in healthy participants. Importantly, the increase in peripheral BDNF concentrations following acute exercise has been shown to remain elevated following conclusion of the exercise but returns to baseline levels between 10–60 minutes. Investigating the neurobiological changes that may modulate these acute effects over time, will help in deepening the understanding of the long-term structural and physiological changes that have been described following long-term exercise interventions. It may also help to determine optimal strategies to maximise the effects of both acute and chronic exercise on brain functioning in individuals with MCI.

Exercise-driven increases in BDNF levels are controlled by neuronal activity, neurotransmitters and interactions with peripheral factors that include oestrogen, corticosterone and possibly Insulin Growth Factor-1 (IGF-1) (Cotman and Berchtold, 2002). It is known that BDNF expression is modulated by increased oestrogen levels (Singh et al., 1995). In that way, the decline in oestrogen levels in women in the menopause (Simpkins et al., 1997) may result in lower expression of BDNF. Meta-analytic reviews have found a gender-based response of BDNF to exercise with men presenting a greater BDNF response to exercise compared to women (Dinoff et al., 2017, Szuhany et al., 2015). In females, the benefits of exercise appear to depend on the presence of oestrogen (Berchtold et al., 2001), as reduced levels of oestrogen compromise neuronal function, survival and synaptogenesis in animal models (Wise et al., 2001), and decrease hippocampal availability of BDNF (Berchtold et al., 2001, Singh et al., 1995).

While evidence supports strong associations between higher levels of CR fitness and cognitive function (Wong et al., 2015, Smith et al., 2010), the relationship between BDNF and CR fitness is unclear. The majority of observational studies have suggested an inverse relationship between the two variables (Huang et al., 2014, Babaei et al., 2014, Currie et al., 2009, Jung et al., 2011, Cho et al., 2012), while others have shown negligible effects (Swift et al., 2012, Whiteman et al., 2014). One proposed theory underlying this negative association is that highly fit subjects present with elevated resting cortisol levels (Luger et al., 1987, Mastorakos et al., 2005) and high levels of cortisol (induced by high fitness or stress) inhibits hippocampal BDNF production in animal models (Schaaf et al., 2000, Murakami et al., 2005, Grønli et al., 2006). Another proposed theory, is that reduced levels of serum BDNF in more physically active individuals reflects a more efficient uptake mechanism of peripheral BDNF into the central nervous system, hence lowering basal resting levels. However, despite the inverse relationship described between BDNF and CR fitness, a recent meta-analytic review by Dinoff et al. (2017) reported significant associations between VO_2peak and effect sizes in studies measuring the effects of acute exercise on BDNF ($\beta = 3.548$, $P = 0.002$, $df = 23$), indicating greater increases in peripheral BDNF after acute exercise in those with greater CR fitness. Given the conflicting reports, further research is needed to elucidate the relationship between BDNF and CR fitness.

1.7 Acute exercise, BDNF and cognitive performance

Findings from both rodent and human studies suggest upregulation of BDNF as a potential mechanism of the effect of acute exercise on cognition (Gómez-Pinilla et al.,

2002, Vaynman et al., 2004, Van Praag et al., 2005, Griffin et al., 2009). A meta-analytic review examining the effect of exercise on BDNF levels in three exercise paradigms (Szuhany et al., 2015), indicated a moderate ES for increases in BDNF following a single session of exercise (Hedges' g = 0.46, p < 0.001). Interestingly, chronic exercise training intensified the effect of a single session of exercise on BDNF levels (Hedges' g = 0.58, p = 0.02). Finally, results indicated a small effect of chronic exercise on resting BDNF levels (Hedges' g = 0.28, p = 0.005). Increased BDNF in response to exercise has been demonstrated with some studies also reporting simultaneous improvements in cognitive performance (Ferris et al., 2007, Griffin et al., 2011, Tsai et al., 2014b, Winter et al., 2007). Meta-analytic reviews support the beneficial effects of acute exercise on cognitive performance, with reasonably robust effects that are generally small in magnitude (ES = 0.11–0.20) (Chang et al., 2012, Lambourne and Tomporowski, 2010). Studies exploring the acute exercise–BDNF–cognitive performance relationship have had mixed findings, but this may be more reflective of methodological differences between studies than it is a statement about the role of BDNF. For example, significant associations have been observed between acute exercise-induced change in peripheral BDNF concentration and cognitive performance in studies assessing memory while non-significant associations were found in studies assessing non-memory cognitive domains (Piepmeier and Etnier, 2015). Given that memory tasks tend to rely on hippocampal activity, executive functions are frontal lobe-dependent and that the hippocampus is a major area of BDNF expression, it may be that BDNF is only critical to the performance of memory tasks and is not implicated more broadly in explaining the effects of acute exercise on other types of cognitive performance (Piepmeier and Etnier, 2015).

The acute exercise-BDNF response had previously not been studied in an MCI cohort. However, a recent study by Tsai et al. (2018) found an acute bout of 30 minutes aerobic exercise significantly increased serum levels of BDNF and IGF-1 in elderly aMCI individuals, with levels returning to baseline resting levels approximately 20 minutes after exercise. This PhD thesis will provide a more comprehensive analysis on the acute exercise-BDNF and cognitive relationship in an MCI cohort.

1.8 Summary

As discussed throughout this chapter, a growing body of literature suggests that exercise may help slow the progression of cognitive decline in people with MCI, yet very little is known about the effects of acute exercise (a single bout of exercise) on BDNF concentration and cognitive performance in this patient population. The literature

examining the relationship between acute exercise, BDNF and cognition is in its infancy, and while positive effects have been demonstrated in healthy young adult populations, this research is notably lacking in cognitively impaired populations. Exploring the BDNF response to acute and chronic exercise may offer new insights into a mechanism of action underlying the exercise-cognitive relationship in an MCI cohort. Across studies, one component of exercise prescription (modality, duration or intensity) was manipulated to test the impact of manipulating these variables on levels of BDNF concentration and cognitive performance. The overarching aim of this thesis was to investigate the effect of acute (varying modality, duration or intensity) and chronic exercise on serum BDNF concentration and cognitive performance (visuospatial learning and memory, attention and executive function) in a group of sedentary older adults with amnestic type MCI (Table 1-1).

The following Chapter 2: Methodology will discuss the sub-studies specific to the PhD programme, outlining the aim, objective and design of Studies I-V, in addition to an overview of the NeuroExercise study and the integration and alignment of the PhD programme to NeuroExercise.

Table 1-1 Overview of the studies in the PhD programme outlining study title, aims and study type. MCI: Mild Cognitive Impairment. BDNF: Brain Derived Neurotrophic Factor.

Study	Aim	Study type
The effect of structured aerobic exercise on cognitive performance in mild cognitive impairment: a systematic review	• To investigate the effects of structured aerobic exercise training (specific focus on exercise prescription parameters) on cognitive performance in individuals with MCI. • Secondary analysis of the included studies explored blood biomarkers and measures of cardiorespiratory fitness.	Systematic Review
Study I: High intensity acute aerobic exercise effects brain derived neurotrophic factor in mild cognitive impairment: a randomised controlled study	• To investigate the immediate change in serum BDNF and cognitive performance following a short bout of high intensity aerobic exercise compared to a resting control condition. • To explore sex differences in serum BDNF and cognitive performance following an acute bout of high intensity exercise	Randomised Controlled study
Study II: A comparison of contrasting aerobic exercise protocols on serum brain derived neurotrophic factor concentration and cognitive performance in mild cognitive impairment	• To compare the effect of two distinct acute aerobic exercise protocols (short bout high intensity versus longer bout moderate intensity) on serum BDNF concentration and cognitive performance in an MCI cohort	Within subjects Pre post-test design
Study III: An investigation of two distinct acute exercise paradigms on serum brain derived neurotrophic concentration and	• To investigate the effect of two distinct acute exercise modalities (moderate intensity aerobic versus non-aerobic balance and	Experimental study

cognitive performance in mild cognitive impairment	toning) on serum BDNF concentration and cognitive performance in individuals with MCI.	Pre post-test design
Study IV: The impact of acute and chronic exercise on serum brain derived neurotrophic factor concentration and cognitive performance following 6 and 12 weeks of structured exercise training in mild cognitive impairment	• To examine whether 12 weeks of structured aerobic training had a cumulative effect on resting measures of serum BDNF concentration and cognitive performance compared to a balance and toning group. • To explore whether chronic aerobic training increases the magnitude of acute exercise BDNF and cognitive response.	Experimental Study Pre post-test design
Study V: Peripheral brain derived neurotrophic factor and episodic memory in a mild cognitive impairment population: results from a one-year exercise intervention study	• To examine serum BDNF concentration and episodic memory in a group of older adults with amnestic MCI over a 1-year period and to investigate whether there was a difference between three intervention groups (aerobic exercise v balance and toning v control). • To investigate change in cardiorespiratory fitness (VO_2max) in an MCI cohort over a one-year period and explore whether participation in a structured exercise intervention lead to changes in cardiorespiratory fitness compared to a control group	Interventional study with 1-year follow-up

2 Chapter 2: Methodology

2.1 Introduction

This chapter will describe study design, sampling methods, data analysis and the background to assessment procedures used across studies I-V, presented in Chapters 4-8 in this thesis. Several assessments are common to all studies and subsequent chapters will refer back to the relevant sections in this chapter when describing individual study methods.

The studies discussed in this thesis were designed as a number of sub-studies to the NeuroExercise study. As such, participant selection criteria was uniform across studies and will be discussed in this chapter to limit duplication in later chapters. The NeuroExercise study is a European multi-centre Randomised Controlled Trial (RCT) examining 'The effects of an extensive exercise programme on the progression of Mild Cognitive Impairment (MCI): study protocol for a randomised controlled trial' (Devenney et al., 2017). The protocol paper for the NeuroExercise study, which was written by the author of this thesis (KD), was published in BMC Geriatrics and is available in Appendix I. I was study coordinator at the Dublin site and had responsibility for overseeing study implementation.

The NeuroExercise study recruited from the German Sports University in Cologne, Radboud University Medical Centre in Nijmegen, the Netherlands and Trinity College Dublin. In the NeuroExercise study, participants (target accrual of 75 at each site) were randomised to either a yearlong aerobic exercise (AT) intervention, balance and toning (BAT) (non-aerobic) exercise intervention or control group. The primary outcome was change in cognitive performance as measured by a neuropsychological test battery. Secondary outcomes included measures of cardiovascular fitness, physical activity, epigenetics, quality of life and measures of frailty.

The aim of this PhD thesis was to examine the effect of acute exercise (varying intensity, type and duration), within the context of a chronic exercise intervention and, on peripheral BDNF concentration and cognitive performance in people with MCI. The NeuroExercise study is described in detail in section 2.3 of this chapter.

2.2 Background research methods

2.2.1 Study designs

Two broadly defined types of studies are reported in health research: observational and experimental. There are three main types of observational studies that are distinguished by the study objective, sampling methods and the timeline of data collection. These are cross-sectional, case-control, and cohort studies which have been widely utilised in clinical research to answer observational research questions.

In observational studies, the inability to control for confounding variables is a considerable limitation. A confounding variable is independently associated with both the variable of interest and the outcome and may provide an explanation for the result (Mann, 2003). In addition, because the exposure and outcome are simultaneously assessed, there is generally no evidence of a temporal relationship between exposure and outcome. Observational studies possess an ability to address a broader range of questions with results more likely to include a broad representation of the population at risk.

Experimental design (randomised or non-randomised) refers to studies in which the investigator assigns an exposure to a group and may further compare the outcome of this exposure to a control group. Experimental studies can be subdivided into randomised and non-randomised trials (Grimes and Schulz, 2002). In experimental studies, the randomised controlled trial (RCT) is considered the most reliable research design to test interventions (Riffenburgh, 2012, Stel et al., 2007). Randomised controlled trials (RCTs) were first introduced into clinical medicine in 1948 when streptomycin was evaluated in the treatment of tuberculosis. Since then, RCTs are widely regarded as the gold standard in clinical research as the randomisation procedure controls for confounding variables and help to eliminate selection bias, both important methodological issues observed in trials.

The quantitative studies of this thesis are experimental in nature. Study I is a randomised controlled study and studies II – V have a pre-post-test design. The design of each study with be discussed within the relevant chapters.

2.2.2 Sampling

An adequate sampling method and sufficient sample size are necessary in quantitative research to ensure that statistical results can be detected, findings have external validity and can be generally applied to the population of interest (Fox et al., 2007). Statistical work in health research typically involves using a sample to draw conclusions from a larger population. To this end, it is necessary to utilise a means of reducing the number of participants in a study without increasing the risk of bias. Random or probability sampling are sampling methods used in a specific populations with the aim of reducing selection bias (Bland, 2015, Riffenburgh, 2012). The probability that a member of the population will be chosen for the sample is purely by chance. The list from which the sample is to be drawn is referred to as the sampling frame (Bland, 2015, Carter and Lubinsky, 2016). Random sampling implies that all people within the sampling frame have an equal probability of being selected for the study (Fox et al., 2007).

When random sampling is not possible, non-probability sampling methods are used as an alternative sampling method. As non-probability sampling methods remove the element of random selection, they cannot be fully reflective of a population and are inherently biased. However, these methods can be useful in exploratory research such as pilot studies and are widely used in rehabilitative research (Carter and Lubinsky, 2016). Common non-probability sampling methods include convenience sampling, quota sampling, purposive sampling, and self-selection sampling. In this PhD thesis, purposive criterion and self-selection sampling were used as sampling methods and these will be discussed in later chapters.

When planning a study, a key consideration is the number of participants and observations required to adequately answer the research question. Too many unnecessary observations wastes resource, while too few will reduce the power of the study (Suresh and Chandrashekara, 2012). The objective during sample size calculation is to find a balance between the risk of a type I or type II error occurring. A type I error (α) occurs when the null hypothesis is rejected when it is true. A type II error (β) occurs when the null hypothesis is accepted when it is in fact false (Bland, 2015).

Calculation of sample size involves specification of a number of parameters including:

- An estimate of the standard deviation is required to give indication of magnitude of chance variation.
- It must be specified whether a one or two-sided test is required.

- A significance level (α) i.e. risk of type I error must be defined. Conventionally 0.05 and 0.01 are used.
- The minimal important difference (∆) of the outcome of interest must be specified.
- The power (1- β) of the test must be determined. A powerful test is one which has a high probability of rejecting the null hypothesis when it is false. Most studies aim to have a power of 80% or higher (Riffenburgh, 2012, Mullins, 2003).

2.2.3 Reliability and validity

In quantitative research, reliability and validity are often used when assessing research rigour. Reliability relates to the stability of findings while validity is concerned with the truthfulness of findings (Carpenter and Suto, 2008).

2.2.3.1 Reliability

Reliability is regarded as the credibility and consistency of research findings and is often related to whether findings are free from measurement error when repeated under identical conditions (McDowell and Newell, 1996). Reliability can be described in term of relative and absolute reliability. Relative reliability, reported as inter-rater and intra-rater reliability examines the relationship between two or more sets of repeated measures and informs us about the error that may exist in an outcome measure (Huang et al., 2011). Intra-rater reliability describes the extent to which the same person can rate the same performance consistently. Inter-rater reliability describes the extent to which different people rate the same performance consistently.

2.2.3.2 Validity

Validity is concerned with the integrity of measurement and refers to the degree to which a scale measures what it is intended to measure (Bryman, 2015). Evaluating the validity of a tool is especially important when measuring constructs that are not directly observable (Liamputtong, 2013). Validity is not inherent to an instrument and is best evaluated within the context of a test's intended use and specific population (Streiner et al., 2015). Methods and types of validity that are commonly evaluated include: content, construct and criterion validity (Liamputtong, 2013).

2.2.4 Principles of data analysis in quantitative research

Quantitative health research involves the measurement of health phenomena with the resulting data commonly summarised and analysed using statistics. Firstly, descriptive statistics are used to summarise data and interferential statistics are then used to

analyse the data. Descriptive statistics include measures of central tendency (the mean (M) and the median (Md)), and measures of dispersion (the standard deviation (SD) and interquartile range (IQR)). Categorical variables (derived from nominal or ordinal data) are analysed using frequencies or the percentage of frequencies. Descriptive statistics for categorical variables are presented in pie-charts and bar charts. Continuous variables (scale data) are described by a measure of central tendency (mean, median, and mode) and a measure of variation around the mean / median (standard deviation / interquartile range). Graphically descriptive statistics for continuous data can be presented in histograms or boxplots. Descriptive statistics for continuous variables provide information regarding the distribution of scores. Skewness refers to the symmetry of the distribution and kurtosis gives an indication of the peak of the distribution (Pallant, 2016).

Data normality is an underlying assumption in parametric testing and it illustrated by a normal curve around the mean. An assessment of normality of data us a prerequisite for many statistical tests. Normality can be identified through the visual interpretation of the descriptive data including normality Q-Q plots and histograms. Normality can also be assessed through numerical methods such as the Shapiro-Wilk test. The Shapiro-Wilk test assesses if data is normally distributed for each independent variable and is recommended in small sample sizes of (<50 participants). The statistical result of the test indicates whether the data is normally distributed ($p > 0.05$) or not normally distributed ($p < 0.05$). In the case of non-normally distributed data, log transformations can be applied to achieve log-normality or non-parametric tests can be used. Normally distributed data is described as mean (standard deviation) and non-normally distributed data is described as median (inter-quartile range).

Statistical tests can be utilised to compare differences in continuous variables between groups. Parametric tests include the independent-samples t-test, the paired-samples t-test, and analysis of variance (ANOVA). The non-parametric alternatives to these tests are the Mann-Whitney U Test, Wilcoxon Signed Rank Test, and the Kruskal-Wallis Test (Pallant, 2016, Bland, 2015, Riffenburgh, 2012). Statistical significance testing considers if an observed difference is sufficiently large enough to warrant concluding the existence of a systematic difference from a hypothesised value. With statistical testing, the hypothesis to be tested is referred to as the null hypothesis (H_0), it is assumed to be true unless the statistical test clearly demonstrates otherwise. The alternative hypothesis is labelled H_1. If H_0 is rejected the test is deemed to be statistically significant (Mullins, 2003). A p-value is an estimate of the probability of getting the observed results when the null hypothesis is true. The significance level of a test is referred to as alpha (α), and

is the value below which the difference between groups is not likely due to chance. Alpha is most commonly set at 0.05. A p-value of >0.05 indicates a non-significant result and that the null hypothesis should not be rejected. A p-value of <0.05 indicates a statistically significant result and that the null hypothesis should be rejected. Alternatively, confidence intervals which represent the spread of the data can be used to determine statistical significance. Confidence limits are typically set at 0.95 (95% CI). In statistical testing 95% CIs which do not contain zero are deemed to be statistically significant at the 5% level (Gardner and Altman, 1986).

Relationships between variables can be analysed using correlations and regression analysis. Correlations coefficients are used to summarise the degree of relationship (correlation) between variables. The value of correlation coefficient ranges from + 1 (perfect positive correlation), through 0 (no correlation), to -1 (a perfect negative correlation). In health research, the Pearson correlation coefficient (interval or ratio) and the Spearman's correlation coefficient (non-parametric, mixed levels of measurement) are commonly used. Multiple regression analysis involves a multivariate procedure that assesses the degree to which scores for a subset of variables predict scores for another variable in the set.

2.2.5 Statistical approach in this thesis

Data analysis was performed in all studies in this thesis using IBM SPSS Statistics version 24 (SPSS Inc, Chicago, IL). Preliminary analyses were performed to ensure no violation of the assumptions of normality by visual inspection of histogram and Q-Q plots and using Kolmogorov-Smirnov test (p>.05). Normally distributed data are presented as means (SD) and non-normally distributed data as medians (IQR). Categorical variables are presented as frequency (percentage). Change in BDNF concentrations and cognitive performance from pre-post each exercise bout was examined using paired sample t-tests for repeated measures on each patient and independent samples t-test for comparison between two exercise states. Non-parametric tests were used if data was not normally distributed. Correlations between BDNF and cognition were examined using Pearson Product Moment correlations or Spearman's rho correlations as appropriate. Significance is taken at p<0.05.

To standardised baseline data, BDNF data was examined for outliers, with measurements ± 2 Standard Deviations (SD) removed from the mean excluded as per standard approach (Griffin et al., 2011). Secondly, relative change (%) in BDNF was

reported as appropriate, consistent with published reports (Knaepen et al., 2010, Saucedo Marquez et al., 2015).

A power analysis on the primary outcome (BDNF) was performed in study I, Chapter 4. As all other studies within this thesis were considered exploratory work and nested within the larger NeuroExercise trial, a power calculation was not performed. Full details of statistical analysis for each study is presented in the relevant chapters.

2.3 Overview of the NeuroExercise Study

Within the NeuroExercise study, the author (KD) had the responsibility for overseeing study implementation and coordination at the Dublin site. Duties included ethics submission at each site, participant screening and recruitment, study assessments, implementation of the 12-month NeuroExercise exercise protocol, data management, data analysis and liaising with local referring sites and international partners. Recruitment began in January 2016 and the final study assessment was complete in August 2018.

2.3.1 Ethics approval

Ethical approval for the NeuroExercise Study and all studies within the PhD programme was obtained from the joint St. James's / Tallaght Hospital Joint Research and Ethics Committee (REC) (Appendix IV). In addition, REC approval was obtained from Mater Misericordiae University Hospital, St. Vincent's University Hospital and St. Patrick's University Hospital which were referral sites to the NeuroExercise study (Appendix V). All procedures were performed in accordance with the 1964 Helsinki declaration and its later amendments. All researchers completed training in Good Clinical Practice and General Data Protection Regulation provided by Wellcome Trust Health Research Board Clinical Research Facility in St. James's Hospital. All participants provided written informed consent (Appendix VI).

2.3.2 Recruitment and screening

Two recruitment strategies were established for the NeuroExercise study in Dublin; a hospital-based recruitment network and a community-based advertisement strategy. A network of external referring sites was established to aid recruitment rates and seven memory clinics in the greater Dublin area were affiliated to the NeuroExercise study at the Dublin site. The community recruitment strategy consisted of study advertisements (Appendix VII) and study posters (Appendix VIII) which appeared in newspapers, parish

newsletters and GP practices around the Dublin area. In both recruitment strategies, initial screening was completed over the telephone to determine eligibility. Participants were then invited to a face-to-face screening appointment and those who met the defined diagnostic, inclusion and exclusion criteria and successfully completed all baseline measures were enrolled. Using these methods, 62 previously sedentary adults aged 50 years or older meeting MCI diagnostic criteria were recruited to the NeuroExercise study at St. James's Hospital Dublin (Table 2:1).

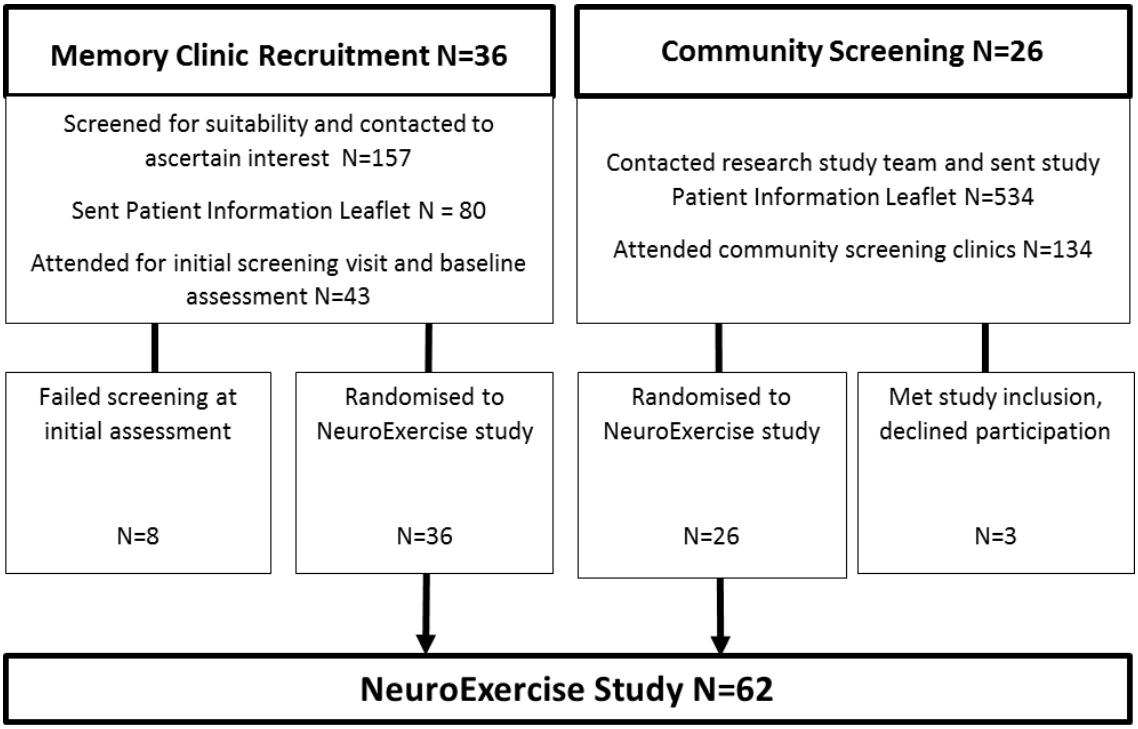

Figure 2:1 Recruitment, screening and selection of participants to the NeuroExercise Study

2.3.3 Diagnostic criteria

Participants had a diagnosis of MCI due to AD according to the National Institute on Aging and Alzheimer's Association (NIA-AA) criteria (Albert et al., 2011) criteria. All enrolled participants with MCI were classified as having memory decline but not dementia (Clinical Dementia Rating global score = 0.5), consistent with established MCI classification (Albert et al., 2011, Petersen, 2004).

2.3.4 Inclusion criteria

Participants who met the following criteria were eligible to participate in the NeuroExercise study and consequently each of the four sub-studies presented in this thesis: (1) Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005) 18-26; (2)

stable medical condition for more than six months; (3) stable medication for more than three months; (4) adequate visual and auditory acuity to complete neuropsychological testing; (5) electrocardiogram without significant abnormalities that might interfere with the study; (6) physical ability sufficient to allow performance of endurance exercise training; (7) capacity to provide written and dated informed consent form; (8) medical clearance to undergo a symptom-limited cardiopulmonary exercise test and extensive aerobic exercise training.

Participants recruited from the community via newspaper articles and community advertisements completed additional testing to determine MCI status. To distinguish between amnestic and non-amnestic MCI, agreed education adjusted cut-offs of -2 SD for low education (<10 years of education), -1.5 SD for the middle group (10-13 years of education) and -1 SD for the highly educated (>13 years of education) were taken from the delayed recall portion of an age adjusted episodic memory test using the Logical Memory (story recall) subtest of the Wechsler Memory Scale (WMS-IV) (Wechsler, 2014).

2.3.5 Exclusion criteria

Any individual who met any of the following criteria was excluded: (1) diagnosis of AD or other type of dementia; (2) history of familial early-onset dementia; (3) enrollment in any investigational drug study; (4) history in the past two years of epileptic seizures (participants with epilepsy who have been stable off medication or seizure free for two years may be included); (5) any major psychiatric disorder (a clinical diagnosis of major depressive disorder, bipolar or schizophrenia); (6) past history or MRI evidence of brain damage, including significant trauma, stroke, hydrocephalus, mental retardation, or serious neurological disorder; (7) carotid stent or severe stenosis; (8) history of myocardial infarction within previous year; (9) congestive heart failure (New York Heart Association Class II, III or IV) (10) uncontrolled hypertension or hypotension (systolic blood pressure >200 mm Hg and/or diastolic blood pressure >110 mm Hg at rest); (11) unstable cardiac, renal, lung, liver, or other severe chronic disease; (12) type II diabetes mellitus with hypoglycemia in the last 3 months; (13) significant history of alcoholism or drug abuse within last 10 years; (14) engagement in moderate-intensity aerobic exercise training for more than 30 minutes, 3 times per week, during past 2 years; (15) history of vitamin B12 deficiency or hypothyroidism (stable treatment for at least three months is allowed); (16) serious or non-healing wound, ulcer, or bone fracture.

2.3.6 NeuroExercise intervention

Participants in the NeuroExercise study were randomised to one of three groups. Following baseline assessment (T0), participants were randomised to one of three arms using a centrally controlled computer-generated randomisation list generated by an independent statistician. Investigators were blinded to allocation order and the treatment was assigned using sealed envelopes based on order of recruitment. Study outcome assessors were not blinded to the allocated treatment arm. Participants were randomised to either a 48-week (3 units of 45min / week) aerobic exercise (AT) (n=19), equivalent balance and toning (BAT) intervention (n=22) or to the control group (n=21) as part of the NeuroExerise study. The aim of the exercise intervention groups was to complete 3 x 45-minute exercise sessions per week. Exercise sessions were supervised twice weekly for the first 8 weeks and once weekly thereafter. Participants completed unsupervised exercise sessions at home as instructed by the supervising physiotherapist. Participants were instructed to record unsupervised sessions using a home exercise diary (Appendix IX). This information was collected and logged by the study exercise trainer each week at the supervised exercise session.

2.3.7 Relationship between the NeuroExercise Study and this thesis.

For this thesis, participants with MCI, recruited to participate in the NeuroExercise study completed blood sampling and cognitive measures pre and post separate and controlled acute exercise conditions. These will be discussed below and related to relevant studies. See Figure 2:4 for a pictorial timeline outlining how PhD studies relate to the NeuroExercise Study.

2.4 Exercise conditions

2.4.1 Exercise condition 1: Short bout high intensity aerobic exercise

A short bout of high intensity (maximal) exercise was used to examine the research questions presented in Study I, Study II and Study V. This exercise condition was a graded exercise test which formed part of the baseline and exit assessment of cardiorespiratory (CR) fitness for NeuroExercise study participants. Cardiopulmonary Exercise Testing (CPET) measuring maximal oxygen uptake VO_2max is considered the most reliable measurement of CR fitness (Agnew, 2010). CPET is considered safe with recent data reporting risk of serious complications <2 per 10,000 tests performed (Myers et al., 2002). Attention to contraindications for exercise testing, careful monitoring during the test and knowledge of the test termination criteria were adhered to for improved

safety (ACSM, 2010). Prior to performing a CPET, a number of aspects of testing were determined including the equipment to be utilised and the test protocol.

2.4.1.1 Safety considerations

Each CPET was administered by a physiotherapist who was experienced in exercise testing. The study doctor, Dr Damien Ferguson, Neurology Registrar was also present for the duration of the CPET and provided medical clearance for study participants to participate in exercise testing and training. Prior to participating in the CPET, all participants were screened for contraindications to exercise testing and prescription. Absolute and relative indications for stopping exercise (both testing and training) are provided in (Table 2-1, Appendix X).

At the start of screening, participants were required to answer a number of questions pertaining to their medical history and answers were recorded on a case report form (Appendix XII). This included questions with regard to cardiovascular disease, respiratory disease, diabetes, orthopaedic conditions, neurological conditions and any other medical conditions that may impact on their ability to exercise safely. Participant's current medications were also recorded. Baseline assessment of cardiovascular status included resting heart rate (HR), blood pressure (BP) measurement (seated and standing), and oxygen saturations. Participants had a resting 12- Lead Electrocardiogram (ECG) (Philips PageWriter TC70 Cardiograph, USA) in advance of all CPETs. The CPET was not performed if the doctor identified any ECG abnormalities which are contraindications to exercise testing. In line with NeuroExercise study protocol, any case of BP measurements outside the acceptable range (resting systolic BP > 200 mmHg and/or diastolic BP > 110mmHg), arrthymias on ECG (ACSM, 2010) or room air saturations < 85% at rest (ATS/ACCP, 2003), the CPET was not performed and participants were referred to appropriate follow up services.

All CPETs took place in the Wellcome Trust - Health Research Board (HRB) Clinical Research Facility (CRF) at St James's Hospital (SJH). The CRF is a dedicated research centre within SJH which is staffed by research nurses. Crash trolley facilities are available within the CRF, and the CRF is serviced by the SJH crash team. All members of the research team were up to date basic life support (BLS) training prior to commencing work in the CRF. All researchers were also required to complete a structured induction to the CRF which included instructions in the event of an emergency.

Table 2-1 American College of Sports Medicine (ACSM, 2010) indications for stopping exercise testing

Indicators for Stopping Exercise

Absolute indications for Stopping Exercise:
• Suspicion of a myocardial infarction or acute myocardial infarction (heart attack)
• Onset of moderate-to-severe angina (chest pain)
• Drop in systolic blood pressure (SBP) below standing resting pressure or drop in SBP with increasing workload accompanied by signs or symptoms
  o Hypotensive response resulting in SBP <60mmHg
• Signs of poor perfusion (circulation or blood flow) including pallor (pale appearance to the skin), cyanosis (bluish discoloration) or cold and clammy skin
• Severe or unusual shortness of breath
• CNS (central nervous system) symptoms
  o Ataxia (failure of muscular coordination)
  o Vertigo (an illusion of dizzying movement)
  o Visual or gait (pattern of walking or running) problems
  o Confusion
• Patient's request to stop
• Irregular pulse
• Extreme fatigue

Relative Indications: • Increasing chest pain • Physical or verbal manifestations of shortness of breath or severe fatigue • Wheezing • Leg cramps or intermittent claudication (grade 3 on a 4-point scale) • Hypertensive response

2.4.1.2 Cycle ergometer testing protocol

The CPET was performed on a standard COSMED cycle ergometer and progressed according to the WHO protocol (Fletcher et al., 2001). While cycle ergometers and treadmills are both commonly used for exercise testing, a cycle ergometer test was chosen as it offered the advantage of being able to reliably record and monitor BP and ECG measurements during exercise (Gormley and Hussey, 2009). However, during cycle ergometer testing the quadriceps are prone to discomfort and fatigue which can

result in earlier test termination (Vanhees et al., 2005). Walking is for most people a more familiar and comfortable form of exercise, and therefore treadmill testing is often the preferred testing method (ACSM, 2010, Hussey, 2005, ATS/ACCP, 2003). However, VO_2max has also been found to be overestimated by 5-10% when assessed using a treadmill test (ATS/ACCP, 2003). VO_2max is 10% to 20% lower in cycle versus treadmill testing in those not accustomed to cycling (Fletcher 2013).

2.4.1.3 Indirect Calorimetry

The measurement of oxygen consumption during all CPETs was performed using the $K4B^2$ equipment ($K4B^2$ User Manual, Cosmed, Italy) (Figure 2:2). Prior to testing both the turbine and the gas analyser (sampling line) were calibrated. The turbine was calibrated using a 3-litre calibration syringe, this was to update the gain of the flowmeter. Calibration of the gas analyser involved 3 separate tests:

1. Room Air Calibration. Room air was sampled and the baseline CO_2 analyser was updated to the gain of the O_2 analyser to match predicted atmospheric values.
2. Reference Gas Calibration. A gas of known composition (5% CO_2, 16% O_2,) was sampled from a cylinder and updated baseline and gain of analysers to match predicted values of gases.
3. Delay Calibration. Requires the tester to breath in and out of the device. This measures accurately the time necessary for gas to pass through the sampling line.

Figure 2:2 Cosmed bike and K4B2 equipment

The height of the cycle ergometer (COSMED ergoline GMbH, Germany) was adjusted to a suitable height for each participant. The testing protocol was explained to participants prior to commencing the test. Blood lactate measurement was taken at rest, during the second stage of the test and upon test completion, using a lactate monitor (Lactate Plus, Lactate Meter, NovaBiomedical, UK).

2.4.1.4 Study protocol and CPET procedure

The WHO protocol, an incremental cycle ergometry testing protocol, is considered an appropriate exercise test as it includes the recommended low intensity warm-up phase followed by progressive, continuous exercise where subjects typically reached maximal levels between 8 – 12 minutes (Wasserman 1994). The test commences with a 3 minutes warm-up period in which participants cycle unloaded, followed by an incremental phase of exercise during which the load increased by 25 watts every 2 minutes until the test is terminated (Figure 2:3). The height of the seat was adjusted so that the knee was slightly flexed (about 25 degrees) with maximal leg extension with the ball of the foot on the pedal. The workload was raised through increases in the resistance on the flywheel. Participants maintained a constant pedalling cadence between 50-60 repetitions per minute. A built in speedometer displayed individual pedalling rate. The speedometer was checked by the lead investigator to ensure that the participant maintained a constant pedalling frequency throughout the test. Gas exchange during the test was measured by indirect calorimetry. BP was assessed every 4 minutes manually using a sphygmomanometer (Welch Allyn) and stethoscope. ECG was monitored throughout the test and HR was recorded every minute. The test was terminated when three out of four of the following criteria were met:

- Clinical signs of exhaustion
- Respiratory Exchange Ratio >= 1.10
- Within 10 beats of the predicted heart rate (=220-age)
- Flattening of the VO_2 (maximal oxygen uptake) curve (<= 110 ml increase during the last minute)

Participants were verbally encouraged to maintain the pedalling cadence and to give their maximal effort as they approached the end of the test. On termination of exercise, the participant remained seated on the cycle ergometer and continued pedalling unloaded for three minutes to allow the heart rate to return to resting levels. When the test was complete, HR, BP, and oxygen saturations were measured at 1, 3 and 10 minutes post-test completion.

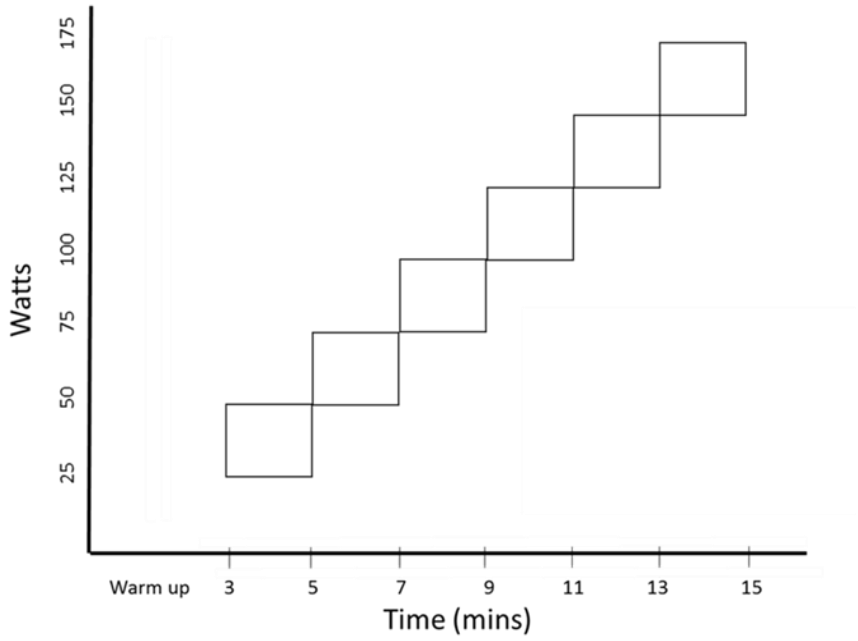

Figure 2:3 WHO exercise test progression

2.4.1.5 Analysis

Data analysis was performed using the COSMED K4B2 software. The software utilises programme algorithms and presents measured data to the specifications of the American Thoracic Society (ATS) and European Respiratory Society (ERS) (COSMED, 2003). Using the COSMED software, the CPET performed at baseline and one year later at the exit assessment from the NeuorExercise study facilitated calculation of the CR fitness (VO_2max) of all study participants at baseline and one year follow up.

2.4.1.6 Exercise prescription

Following baseline assessment, participants on the NeuroExecise study were randomised to an aerobic exercise group, balance and toning exercise group or control group. Participants in both exercise arms were involved in studies I-V in this thesis, while participants randomised to the control group participated in study I and V. All supervised classes took place at the Wellcome Trust– HRB Clinical Research Facility at St. James's Hospital and were supervised by a member of the research team. A case report form was completed during the supervised exercise classes (Appendix XIII). The components of exercise prescription are described below using the FITT principle: Frequency, Intensity, Time (duration) and Type (ACSM, 2010) (Table 2-2).

Table 2-2 Components of exercise prescription are described using the FITT principle: Frequency, Intensity, Time (duration) and Type (ACSM, 2010).

	Aerobic	Balance and Toning
Frequency	3 times per week Week 1-8: 2 supervised sessions and 1 unsupervised session Week 8 – 12: 1 supervised and 2 unsupervised sessions	3 times per week Week 1-8: 2 supervised sessions and 1 unsupervised session Week 8 – 12: 1 supervised and 2 unsupervised sessions
Intensity	Moderate Heart rate 180-age BORG Rate of Perceived Exertion 13	Low BORG Rate of Perceived Exertion <10
Time	45 minutes 5 minute warm up and cool down	45 minutes 5 minute warm up and cool down
Type	Treadmill walking Cycle ergometer Elliptical Training	Balance Yoga Stretching Light resistance

2.4.2 Exercise condition 2: 45 minutes moderate intensity aerobic exercise

The aerobic exercise condition described below was used across studies II, III, IV and V in this thesis. To answer the research questions of the above studies, blood samples were collected and cognitive tests were performed at rest and immediately following the supervised 45 minute moderate intensity aerobic exercise condition during week 1, 6 and 12 of the intervention period.

The goal of the aerobic exercise class was to accumulate at least 45 minutes of aerobic exercise, prescribed by HR calculated as 180bpm – age. Exercise intensity was monitored during the supervised classes using a HR monitor and subjective reporting of the exercise intensity using the Borg's Rating of Perceived Exertion (RPE) (Borg, 1998) (Appendix XI). Borg's rating of perceived exertion (RPE) is a widely used psycho-physical tool to assess subjective perception of effort during exercise. The original 15-point scale is most often used (from 6 no exertion at all to 20 maximal exertion). The

BORG is a well-accepted, easy to use and valuable method for assessing relative effort exerted during exercise (Scherr et al., 2013). Its relationship with physiological and psychological responses across a number of patient population have been extensively researched (Borg, 1982) and have been strongly associated with breathing rate, oxygen consumption and lactic acid level (Gormley and Hussey, 2009), and more closely linked to oxygen consumption than heart rate (Dishman et al., 1994). The aerobic exercise condition comprised of a 5-10 minute warm up, 45 minutes of targeted aerobic exercise and a 5-10 minute cool down. A range of aerobic exercise modalities aware offered including cycling, treadmill walking and elliptical training. Participants in the aerobic exercise group aim to achieve a target RPE of 13 while exercising.

2.4.3 Exercise condition 3: 45 minutes balance and toning exercise (non-aerobic)

The balance and toning exercise condition described below was used across studies III, IV and V in this thesis. The blood sampling and cognitive tests were performed at rest and immediately following the supervised 45-minute balance and toning during week 1, 6 and 12 of the intervention period.

The aim of the balance and toning group was to complete largely non-aerobic activities. Each supervised class comprised of a 5-10 minute warm up, 45 minutes of yoga, stretching, balance, coordination, relaxation, group games, light resistance exercises and a 5-10 minute cool down. During the balance and toning class, exercise intensity was kept equal to or below an RPE of 10. Participants in the balance and toning group were not advised about aerobic activity and were not instructed to avoid completing routine aerobic activity.

Typically exercise intervention studies in patients with MCI compare improvements from the exercise intervention to an active control group in which participants engage in non-aerobic activities (balance, stretching and toning) for an equivalent amount of time. The stretching and toning (non-aerobic) group was designed as an active control group, controlling for the social effect of a structured group exercise programme. This type of low-intensity exercise intervention has previously shown some small positive effects on cognitive outcomes, as it provides participants with equivalent opportunity for social interaction (Unger et al., 1997). Previous exercise intervention studies in MCI that have utilised non-aerobic exercise (e.g. stretching and toning) as a control intervention have noted some improvements in cognitive performance (Heyn et al., 2004, Lam et al., 2011)

while others have not observed significant change in cognitive performance (Baker et al., 2010b, Nagamatsu et al., 2013a).

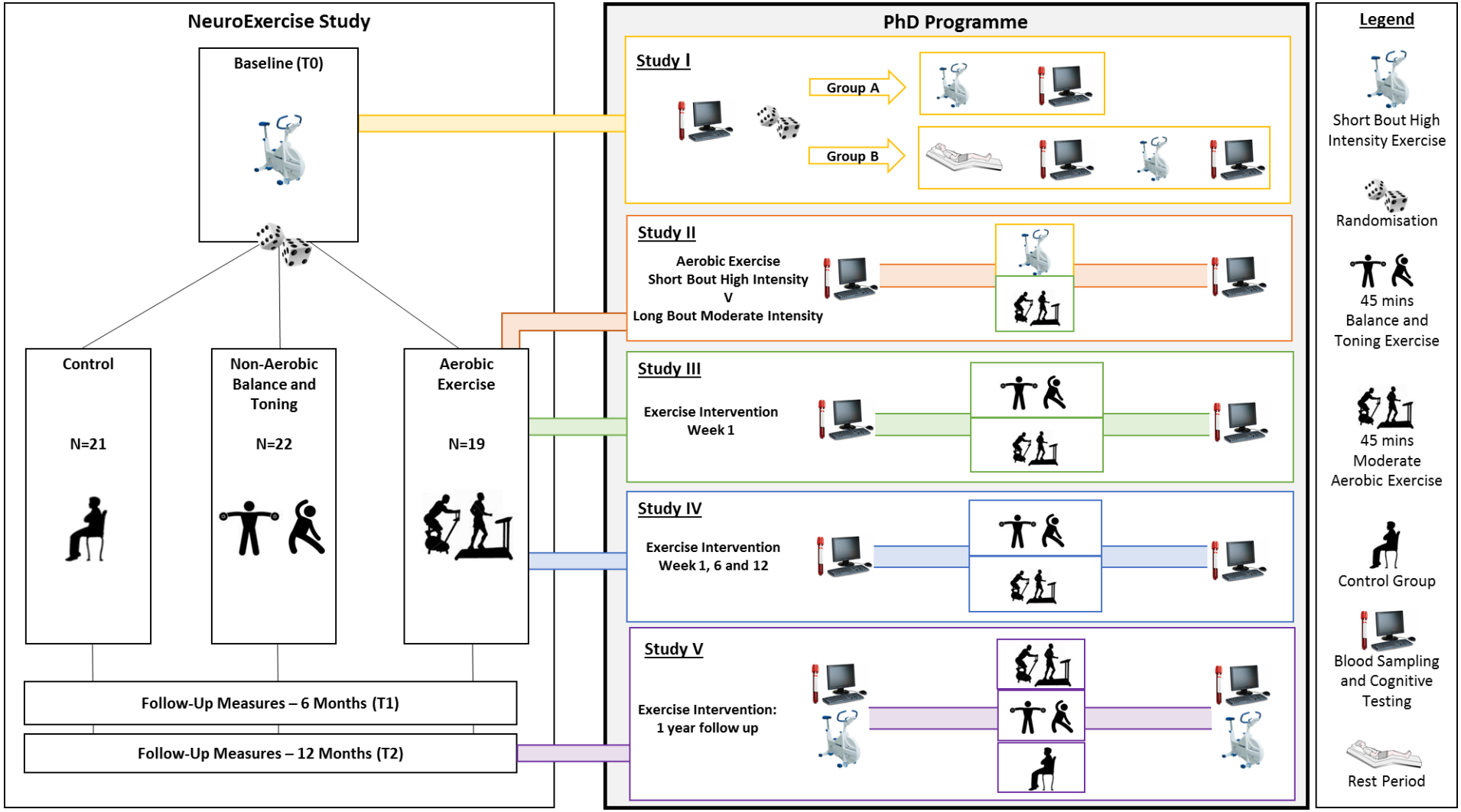

Figure 2:4 Timeline outlining PhD studies relative to the NeuroExercise Study

2.5 Materials

The following section will outline sampling methods and background to assessments for all studies within this thesis.

2.5.1 Blood sampling

2.5.2 Blood collection

Across all studies in this thesis, venous blood samples were drawn by a trained phlebotomist (KD) pre and post exercise. A tourniquet was applied to the arm and venous blood was taken using a sterile 23G Butterfly® needle (Greiner Bio-one ®) and a Vacutainer® system with a luer adaptor (Greiner Bio-one Vacuette®). Samples were drawn into sterile SST™ gel and clot activator and Ethylenediamine Tetraacetic Acid (EDTA) tubes, respectively. Post-exercise blood sampling was collected between 0-10 minutes following completion of the exercise condition. 2 x 5ml serum and 1 x 3ml plasma samples were collected at each time point. Serum and plasma collection tubes were inverted 5 times and allowed to coagulate at room temperature before being centrifuged at 1300 x g for 10 min at 4°C. The resulting serum was removed, aliquoted and stored at -80°C pending laboratory analysis.

2.5.3 BDNF analysis

Laboratory analysis of serum samples was carried out in collaboration with the Department of Physiology, School of Medicine & Trinity College Institute of Neuroscience, Trinity College Dublin. Our collaborating partners, Dr Áine Kelly and Dr Bibiana Mota both have considerable experience in BDNF analysis in animal and human studies and have been widely published within this research field (Griffin et al., 2009, Griffin et al., 2011, O'Callaghan et al., 2007, Callaghan and Kelly, 2012, Callaghan and Kelly, 2013, Bechara et al., 2014). Both Dr Áine Kelly and Dr Bibiana Mota had overall responsibility for the BDNF analysis.

2.5.4 Enzyme linked immunosorbent assay (ELISA)

This technique was used to examine the concentration of BDNF in blood serum samples. Samples and standards were analysed using commercially available BDNF Duoset® ELISA development systems kit (R&D Systems Europe, Oxon, United Kingdom). Standard curve was constructed and concentration of BDNF in samples was calculated by extrapolation from these curves.

For each assay, Nunc Immuno MaxiSorp 96 well plates were coated with capture antibody (see Table 2-3 for concentration), diluted in PBS, 100µl per well), covered and incubated overnight at room temperature with constant agitation. The following day, the plate was washed three times with wash buffer (PBS-T; 0.05% (w/v) of Tween®20 in PBS; 400µl per well; PBS composition: 137mM NaCl; 2.7mM KCl; 8.1mM Na_2HPO_4; 1.5mM KH_2PO_4; pH 7.4) and incubated with reagent diluent (BSA 1% (w/v) in PBS; 100µl per well) for at least 1 hour at room temperature with constant agitation, to block non-specific binding. After the blocking, the plate was washed three times with wash buffer (400µl per well). Standards (diluted with reagent diluent, according to the manufacturer's guidelines; see Table 2-3) and samples, in the prior determined dilution (diluted in reagent diluent), were added in triplicate (100µl per well) and incubated for two hours at room temperature with constant agitation. Plates were washed three times with wash buffer (400µl per well) and incubated with detection antibody (see table for concentration, diluted in reagent diluent, 100µl per well) for two hours at room temperature in constant agitation. The plate was washed three times with wash buffer (400µl per well) and incubated for twenty min at room temperature with Streptavidin-HRP (diluted in reagent diluent; dilution of 1:200,100µl per well). Plates were washed three times with wash buffer (400µl per well) and incubated with the substrate solution (Tetramethylbenzidine - TMB; Sigma Aldrich, Ireland; 100µl per well) in the dark for 20 min at room temperature. The colour reaction was stopped using the stop solution (1M H_2SO_4; 100µl per well). The absorbance of standards and samples was read at 450nm and 540nm on a plate reader (Synergy HT Multi-Mode Microplate Reader, BioTek). The regression equations of the standard curves were constructed for each assay, and concentrations of BDNF was extrapolated from these curves and results were expressed in $pg.ml^{-1.}$

Table 2-3 Capture Antibody Concentration in BDNF analysis

ELISA kit	Capture Antibody	Standard (top standard conc.)	Detection Antibody
Human BDNF	Mouse anti-human BDNF ($2µg.ml^{-1}$)	Recombinant human BDNF ($1500pg.ml^{-1}$)	Biotinylated mouse anti-human BDNF ($25ng.\ ml^{-1}$)

2.5.5 Cognitive testing

A selection of cognitive tests consisting of three separate cognitive measures was administered following each blood draw. Cognitive tests were administered as described below. The cognitive testing took approx. 30 minutes to complete.

2.5.6 Cambridge Neuropsychological Test Automated Batteries (CANTAB): Paired Associate Learning Task

2.5.6.1 Background

The Cambridge Neuropsychological Test Automated Batteries (CANTAB) is a computer-based cognitive assessment system consisting of a battery of neuropsychological tests, administered to subjects using a touch screen computer or tablet. CANTAB is considered one of the most validated and widely used computerised measures of cognition (Robbins et al., 1998). There are 25 tests in the CANTAB repertoire which provide an evaluation of various areas of cognitive function including visual memory, visual attention, working memory and planning (Strauss et al., 2006). Tasks can be ordered and applied individually or as a battery to measure specific aspects of cognitive function across a variety of therapeutic areas. For the studies discussed in this thesis, the CANTAB Paired Associate Leaning (PAL) task, an episodic memory task, was selected and software was ordered from Cambridge Cognition, Tunbridge Court, Bottisham, Cambridge, CB25 9TU, United Kingdom (www.cambridgecognition.com).

Episodic memory is the ability to learn, store, and retrieve information about past experiences and within the realm of animal literature, it is often referred to remembering 'what, when and where' (Barnett et al., 2015). A number of well-validated and reliable human episodic memory tests exist, all differing in important theoretical and practical aspects (Lezak, 2004). The two most common forms are verbal recall tests such as story or wordlist learning, and non-verbal tests such as the CANTAB PAL (Sahakian et al., 1988). CANTAB PAL is considered a visuospatial memory task that assesses visual memory and new learning through the testing of conditional learning of pattern-location associations (Strauss et al., 2006).

2.5.6.2 Task procedure

The CANTAB PAL is a touchscreen iPad-based task in which boxes are displayed on the screen (Figure 2:5) and are opened in a random order, with one or more boxes containing a pattern within. The task instructions are delivered to participants through an automated voice within the PAL programme which provides standardised test

administration. Six white boxes appear equally distributed on the screen and the boxes then open one at a time, for three seconds each in a random order. Initially, only one box contains a pattern with the remaining boxes empty. Once all six boxes have opened and closed, displaying either a pattern or an empty box, the displayed pattern appears in the middle of the screen. The subject is required to touch the box in which the pattern was located. If the subject chooses the correct box, the task proceeds to the next set of patterns. The difficulty level increases through the test with an increasing number of patterns revealed. After two correct sets with a single pattern the number of patterns is increased to two for two sets, then to three for two sets. Finally the number of patterns is increased to six, and then to eight for one set. If the subject makes error, the patterns are displayed again to remind the participant of their locations and the trial is repeated (to a maximum of 10 trials). No feedback for correct responses is given. If a correct response has not been made after 10 trials in any set, the test is terminated. The test takes approximately 10 minutes to complete.

Figure 2:5 iPad interface showing PAL task

2.5.6.3 Scoring

The CANTAB PAL has a total of twenty-one outcome measures. PAL Total Errors Adjusted (PALTEA) refers to the number of times the subject chose the incorrect box for a stimulus on assessment and an adjustment is made for the estimated number of errors they would have made on any problems, attempts and recalls they did not reach. Therefore, the PALTEA value represents the same level attempted for each subject (Sahakian et al., 1988). As this outcome indicates the number of errors made before the completion of the test, a larger score indicates greater difficulty with the task. PALTEA was used as the primary PAL outcome across studies in this thesis (Fowler et al., 1995) (Table 2-4).

Table 2-4 PAL task outcome measured

PAL score	Description
Total Errors (adjusted)	The number of times the participant does not click on a go-trial. A higher score indicates poorer performance on the task

2.5.6.4 Reliability and validity of CANTAB PAL

The psychometric properties, and neural validation, including studies on large samples of healthy volunteers, patients with MCI, and AD have demonstrated consistent validity and reliability of the CANTAB PAL task (Robbins et al., 1994, Fowler et al., 2002, Blackwell et al., 2003). Psychometric properties that make a test suitable for repeated assessment include good test–retest reliability reflecting consistency of measurement over time with minimal practice effects. The CANTAB PAL uses multiple matched stimuli sets and random location of stimuli in order to minimise carry-over from previous assessments and the patterns are designed to be difficult to verbalise, thus discouraging the use of rehearsal strategies (Barnett et al., 2015). One-month retesting using the CANTAB PAL in healthy elderly volunteers was reported to produce relatively minor practice effects of around 0.2 standard deviations in magnitude and good test–retest reliabilities of 0.7–0.9 for the two major outcome measures including PALTEA (Lowe and Rabbitt, 1998).

Test–retest reliability of the PAL test is reported as 0.68 for first trial memory scores and 0.86 for average trials to success in healthy older adults aged between 60 and 82 years (Lowe and Rabbitt, 1998). One-month test–retest reliabilities of 0.71 have been reported in CANTAB PAL total error scores in people with MCI (Fowler et al., 1995). In addition, CANTAB PAL has demonstrated reasonable sensitivity (0.83) and specificity (0.82) in differentiating clinically defined MCI from age-matched healthy controls (Chandler et al., 2008).

2.5.6.5 Clinical studies using CANTAB PAL

CANTAB PAL is highly sensitive to the memory impairments that are characteristic of prodromal AD. In aMCI, the first and most prominent symptom to occur is often impairments in both verbal and nonverbal forms of recognition memory and free recall. These memory impairments arise early in the clinical presentation because they rely heavily on areas affected in the early stages of Alzheimer's neuropathology i.e. the

spread of neurofibrillary tangles and neuropil threads initially in the transentorhinal cortex and then in the entorhinal cortex and hippocampus (Braak and Braak, 1991).

The object-location memory of the PAL task is particularly dependent on integrity of the entorhinal and transentorhinal cortex and hippocampal areas (Parkinson et al., 1988, de Rover et al., 2011). There is also substantial evidence that PAL tasks are sensitive to hippocampal dysfunction and good overall test of hippocampal connectivity (de Rover et al., 2011, Squire, 1992). In healthy older adults, functional neuroimaging studies confirm that the CANTAB PAL task activates the bilateral hippocampus in a load-dependent manner such that activation increases as the number of patterns to be encoded increases (de Rover et al., 2011). Successful performance of the PAL test is dependent on functional integrity of the temporal lobe, particularly the entorhinal cortex, but is also affected by resections of the frontal lobe (Jäkälä et al., 1999). Since the hippocampus has been identified as a major area of BDNF expression and is widely accepted as being vital to the performance of memory, the PAL task is considered a theoretically appropriate method of cognitive task relative to the measurement of BDNF concentration (Hall et al., 2000, Egan et al., 2003).

2.5.7 Sustained Attention to Response Task

2.5.7.1 Background

Sustained attention is a component in most current neuropsychological models of attention (Mirsky et al., 1991, Cohen et al., 1993). Sustained attention refers to the continuous direction of conscious awareness towards specific phenomena and is fundamental for achieving complex goals over time. The ability to sustain mindful, conscious focus on specific stimuli plays a critical role in information processing and is a fundamental precursor to higher order cognitive tasks, including explicit learning and memory formation (Mirsky et al., 1991). It enables the maintenance of vigilance, selective and focused attention, response persistence, and continuous effort despite changing conditions. Originally designed for use in a Traumatic Brain Injury (TBI) population, the Sustained Attention to Response Task (SART) is now a widely used tool in cognitive neuroscience and in brain regions associated with failures of sustained attention. The SART was developed with the intention of providing a brief, reliable, and valid measure of failures of sustained attention related to real-world problems (Robertson et al., 1997, Manly et al., 1999).

Figure 2:6 Laptop displaying SART programme

2.5.7.2 Task

The SART (fixed version), a measure of sustained attention, is a five minute conceptually simple computerised task in which each digit appears for 300ms, with an interval of 800ms between digits (Figure 2:6). The cycle of digits 1–9 is repeated sequentially 23 times, producing a total of 207 trials. The SART is a GO-NO-GO paradigm in which the NO-GO (number 3) target appears rarely. Participants are required to respond to a sequentially presented series of GO digits (1 through 9) and to withhold a response when an infrequent critical NO-GO digit appears (number 3) (Robertson et al., 1997, Manly et al., 1999, Beekman et al., 1995) (Figure 2:7). The SART was administered across studies in this thesis on a laptop using the Neuro-Behavioural Systems Presentation® software (www.neurobs.com). The following instructions were used for SART administration:

1. Now we are going to do a test trying to measure your ability to concentrate. We are going to use the computer in order to do so.
2. In this test, umbers between 1 and 9 will appear on the screen one at a time. They will appear in a fixed order, so you will see a repeating pattern of 1,2,3,4,5,6,7,8,9,1,2… and so on. The numbers will appear on the screen above a fixation cross, which I would like you to focus on during the test. The size of the numbers will vary throughout the test. All you have to do is to click on the left button of the mouse every time you see a number except for number 3.
3. When the number 3 appears, you should not click, just don't do anything and wait for the next number to appear.
4. Now, each number appears for a short amount of time and is followed by a blank screen, which also only stays for a short amount of time before the next number appears. I would like you to left mouse click at

the offset of the number, just as the number is disappearing form the screen.

5. Do not worry about missing some numbers. Everybody makes some mistakes on this test. This is normal. If you make a mistake, there is no need to tell me. You should just continue on with the test.
6. The test is going to be a few minutes long and you may find it a bit boring. Try to do your best to keep your attention up. I will not be talking to you during the test as the test needs to be done in silence. Is that ok? Have you any questions?
7. Let's start with a practice test.

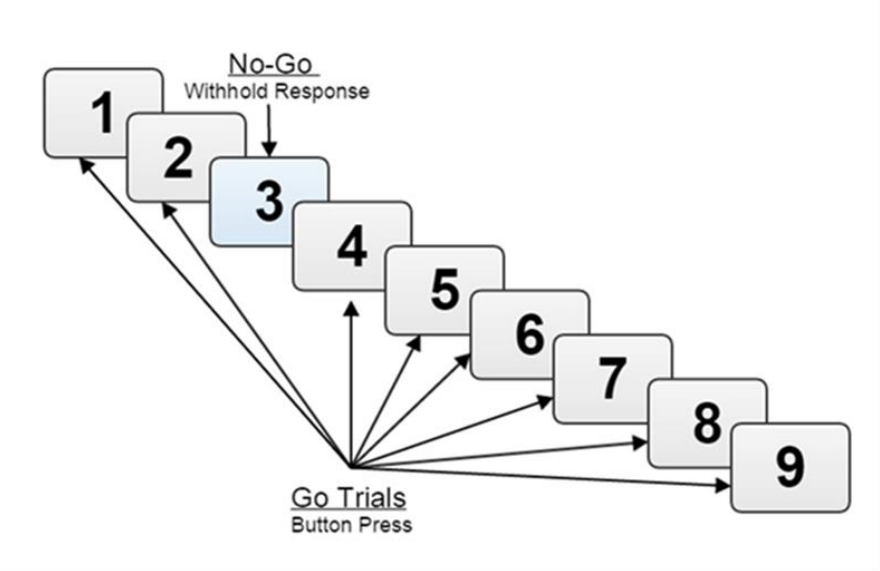

Figure 2:7 Procedure fixed version SART

2.5.7.3 Scoring

Traditional vigilance tasks which measure sustained attention involve active responses to infrequent targets (Cohen et al., 1993). However in the SART, the format of typical vigilance tasks is inverted: participants are required to respond to frequently presented GO stimuli and to withhold their response to infrequent, interspersed NO-GO stimuli. This design in which stimuli are repetitive, monotonous or non-arousing, maintaining sustained attention becomes highly demanding and effortful which in turn leads to habituation and distraction, causing lapses in attention (in response errors and slower reaction time) (Robertson et al., 1997). The following outputs were recorded from each test (see table 2-5).

Table 2-5 SART outcomes

SART score	Description
Commission Errors (CE)	The number of times the participant clicks on Number 3 (NO-GO trial)
Reaction (RT)	Mean and standard deviation of response times to go-trials.

2.5.7.4 Reliability and validity

The SART has shown evidence of good test–retest reliability (r = .76), and stability of SART error rates over a period of two weeks suggesting individual SART performance is relatively stable over time (Robertson et al., 1997). Performance on the SART has been found to correlate with other validated measures of sustained attention (Robertson et al., 1997) and is considered an externally valid measure of an individual's experience of sustained attention failures experienced in everyday life. The validation of the SART was based on positive correlations obtained between SART performance and the Cognitive Failures Questionnaire (CFQ) (Broadbent et al., 1982) with a modest but significant correlation between the CFQ and SART errors for both TBI patients and controls. The validity findings have been replicated by additional studies that provide evidence for a positive association between the CFQ and the number of SART commission errors on NO-GO trials (Linden et al., 2005, Farrin et al., 2003).

2.5.7.5 Clinical studies

The SART has been used to study the neurophysiology of sustained attention, implicating areas such as the anterior cingulate cortex (Cheyne et al., 2009) and both dorsomedial and ventromedial prefrontal cortices, which are two areas associated with the default network (Christoff et al., 2009). MRI Imaging studies during the SART confirmed the activation of the cortical and subcortical attentional networks (O'Connor et al., 2011). Attentional function (also referred to as vigilance) is supported by the arousal system, mediated via a subcortical network involving the thalamus and noradrenergic brain stem structures including the locus coeruleus (O'Halloran et al., 2013), with noradrelaline implicated in attentional function (Fassbender et al., 2004, O'Connor et al., 2011). As degeneration of the locus coeruleus has been observed in patients with MCI and AD, and the associated reduction in noradenaline levels implicated in the progression and extent of cognitive impairment (Grudzien et al., 2007), the SART was considered an appropriate cognitive task relative to the MCI population.

2.5.8 Stroop Neuropsychological Screening Test (SNST)

2.5.8.1 Background

The Stroop paradigm is one of the oldest and most widely used techniques to examine attention and response inhibition (MacLeod, 1991). There are a number of versions available and while the versions differ in the administration, the general principle underlying the task is that in one condition the subject reads aloud a list of colour names in which no name is printed in its matching colour. In another condition, the subject names the colour ink in which the colour names are printed. The Stoop task is considered a measure of executive function and assesses the ability with which a person can maintain a goal in mind and suppress a habitual response in favour of a less familiar one (Strauss et al., 2006). It is most often described as measuring the individual's ability to shift cognitive set, measure cognitive inhibition or the ability to inhibit an overlearned dominant response in favour of an unusual one. The mechanisms underlying the task include working memory, speed of processing information, semantic activation and the ability to strengthen one response characteristic (Strauss et al., 2006).

While multiple versions of the Stroop task exist, the Stroop Neuropsychological Screening Test (SNST) was used across studies in this thesis (Trenerry et al., 1989b). The SNST was developed to provide a standardised method of administration and scoring and was designed to address a number of the methodological and practical issues with previous versions. The SNST assesses a subjects ability to selectively process one visual feature at a time while inhibiting the processing of other features, making it a test of concentration effectiveness (Lezak, 2004).

2.5.8.2 Task

The SNST from Psychological Assessment Resources, Inc. (www.parinc.com) contained the following materials; professional manual, Form C Stimulus Sheets, Form C-W Stimulus sheets and SNST record forms. The Form C Stimulus Sheet consists of 112 colour names (red, green, blue tan) arranged in 4 columns with 28 allocated in each column (see Figure 2:8). The names are printed in one of four different colours of ink (red, green, blue tan) but no name is printed in its matching colour. The form C-W stimulus sheet is the same as the as the Form C Stimulus Sheet, except for the order of the colour names. Participants were administered the Colour Stimulus Sheet and the Colour-Word Stimulus sheet respectively (Appendix XIV).

Figure 2:8 Stroop Neuropsychological Screening Test

The test was administered as per test administration manual (Trenerry et al., 1989a). The subject's ability to accurately identify the four colours in the SNST was assessed and subjects were excluded if they were unable to accurately identify the four colours.

Two tasks were performed and recorded during the administration of the SNST:

1. The Colour Task, requiring the C Stimulus Sheet
2. The Colour-Word Task, requiring the C-W Stimulus Sheet

A stopwatch was used by the administrator and responses were recorded on the record form. The Colour Task while not formally interpreted was administered first to establish if the Colour Task had a priming effect of the degree of interference reflected in the Colour-Word Task. Participants were instructed to read the words aloud as quickly as they could, starting at the top of the first column and to progress through each additional column in the same manner. They were instructed to correct themselves if they made a mistake and keep going. Using a stopwatch, the subject was given 120 seconds to give the responses. The administrator recorded the responses by making a check mark next to each item on the record form. Incorrect responses were recorded by placing an X next to the item. If the subject self-corrected an incorrect response, a C was recorded next to that item. Once 120 seconds had lapsed, the test was stopped and the C Stimulus Sheet

removed. On the interference task, the stimuli are incongruent (e.g., the word “blue” is printed in yellow ink), and the subject must inhibit the prepotent response of reading the word, and read the colour ink in which the word is printed, to respond correctly.

2.5.8.3 Scoring

The CWS score is the primary score used in the interpretation as CWS provides the best classification accuracy and this score is used as a measure of interference (Table 2-6). The CWS is the component that is believed to measure mental flexibility and the ability to inhibit a dominant response (Wecker et al., 2000). It also is believed to provide a measure of the subject’s ability to inhibit stimulus-bound responses and deal with interference.

Table 2-6 Stroop task score and description

SNST score	Description
Colour-Word Score (CWS)	The number of correct responses, or number of items completed minus incorrect responses on the Colour-Word Task. This is similar to the interference score in other versions of the Stroop Task. A higher score indicates improved performance with a greater number of correct responses.

2.5.8.4 Reliability and validity

Reliability and validity data are available in the administration manual (Trenerry et al., 1989). SNST has demonstrated high test-retest reliability (r=.90) (Trenerry et al., 1989b) in a sample of 30 subjects, suggesting high temporal stability. Normative data comes from a sample of 156 adults ranging in age from 18 to 79 and a CWS of < 62 has demonstrated the ability to discriminate between brain-damaged individuals and cognitively intact individuals in the 50 plus age group (Trenerry et al., 1989b).

2.5.8.5 Clinical studies

Impaired executive function is relatively common among older persons with MCI and may be predictive of the development of dementia (Brandt et al., 2009). The failure in inhibitory processes appear to manifest early in the course of AD, with increases observed in the magnitude of the interference effect with as disease severity progresses (Bondi et al., 2002, Koss et al., 1984). Stroop performance is associated with AD pathology in the hippocampus and a number of neocortical regions of the brain including posterior cerebral areas (Bondi et al., 2002, Collette and Van der Linden, 2002). MRI

activation studies performed in healthy adults while performing the Stroop task have demonstrated activation of the frontal regions but also inferior temporal and parietal cortices as well as the caudate nuclei (Brown et al., 1999, Peterson et al., 2002). The frontal brain regions, linked to executive control processes such as planning, inhibition, task switching, maintenance and manipulation of information have shown disproportionate sensitivity to age-related cognitive decline (Goh et al., 2012, West, 1996) but are malleable to aerobic fitness induced cognitive benefit (Colcombe and Kramer, 2003a). A number of studies have demonstrated improved Stroop performance following acute aerobic exercise in cognitively normal adults (Ferris et al., 2007, Yanagisawa et al., 2010).

2.6 Conclusion

This chapter has outlined the procedures for the measures utilised in this thesis. In addition, the exercise conditions used in the upcoming studies have been described. The upcoming results chapters will reference back to this chapter in the descriptions of their methodologies.

3 Chapter 3: The effect of structured aerobic exercise on cognitive performance in individuals with MCI: a systematic review

3.1 Introduction

Robust epidemiological data demonstrates that more physically active individuals show better cognitive performance and a reduced incidence of dementia and AD, compared to sedentary individuals (Hamer and Chida, 2009, Llamas-Velasco et al., 2015, Sofi et al., 2011, Weuve et al., 2004, Yaffe et al., 2001, Hillman et al., 2006), with a similar protective effect in people with MCI (Geda et al., 2010, Lautenschlager et al., 2008). Several meta-analyses found higher levels of physical activity (PA) were associated with improvements across a number of cognitive domains including attention, processing speed and executive function in healthy older adults and in MCI (Angevaren et al., 2008a, Smith et al., 2010, Gates et al., 2013, Heyn et al., 2004). However, despite the volume of epidemiological data, there is a paucity of evidence on the efficacy of structured aerobic exercise programmes and the exercise dose necessary to induce cognitive change in MCI populations.

It is believed that aerobic exercise induced changes in cardiorespiratory (CR) fitness may mediate the exercise-cognitive relationship and help counteract the molecular and cellular alterations underlying the progressive loss of hippocampal function in advanced age and attenuate AD-related brain atrophy (Intlekofer and Cotman, 2013, Erickson et al., 2009, Vidoni et al., 2012). Higher levels of CR fitness have been positively associated with cognitive function in healthy older adults, with the association strongest for measures of global cognition, attention and executive function (Barnes et al., 2003, Etnier et al., 1997). Similarly, high levels of CR are thought to maintain cognitive function in those at an increased risk for AD (Law et al., 2018), and in those with established AD (Morris et al., 2017). Therefore, exercise interventions aimed at increasing CR fitness may represent a modifiable and practical treatment approach to maintaining cognitive function in MCI cohorts.

There is growing interest in the biological mechanisms that may underpin the exercise-cognitive relationship, which remains poorly understood in human studies. One particular theory that has garnered significant attention is that aerobic exercise is neuroprotective, facilitates neuroplasticity and larger hippocampal volumes through a variety of

mechanisms, including the release of trophic factors (Griffin et al., 2011, Brinke et al., 2015, Knaepen et al., 2010, Erickson et al., 2011). Understanding whether aerobic exercise interventions; 1) induce changes in measurable biological markers specific to the pathophysiology of MCI and 2) lead to measureable objective change in CR fitness will help in establishing the efficacy of different types of exercise regimes on cognitive outcomes in MCI. Reviews in this area to date have included very broad inclusion criteria resulting in heterogeneous samples, often combining individuals with subjective memory complaints, considered 'at risk' for future cognitive impairment, and those with a dementia diagnosis. Furthermore, reporting on specific exercise prescription parameters has been lacking in sufficient detail to inform exercise prescription for cognitive benefit. The primary aim of the systematic review was to investigate the effects of structured aerobic exercise training (specific focus on exercise prescription parameters) on cognitive performance in individuals with MCI. To help garner a greater understanding of underlying mechanisms that may underpin the exercise-cognitive relationship in this population, secondary analysis of the included studies in this review explored blood biomarkers and measures of CR fitness.

3.2 Methods

3.2.1 Search strategy

A systematic search of online databases Embase, Pubmed, Cochrane, Psych info, AMED and Cinahl was completed by a university librarian between January 2016 and March 2016, using a range of terms relating to exercise and cognitive performance (Appendix XV). Specifically, the following keywords and Medical Subject Heading terms were used: 'mild cognitive impairment' OR 'cognitive defect' AND 'exercise' AND 'mental function' OR 'cognition assessment' OR 'arousal' OR 'task performance' OR 'perception' OR 'therapy effect' OR 'outcome assessment' OR 'neuropsychological test'. Additional studies were obtained from a manual search of the reference lists of articles, systematic reviews and conference proceedings identified from the online search. Methods and reporting followed the PRISMA preferred reporting items for systematic reviews (Moher et al., 2009).

3.2.2 Inclusion criteria

Studies that met the following criteria were selected for inclusion: defined MCI criteria, structured aerobic exercise training (>6 weeks duration) and measurement of cognitive performance as the primary outcome.

Studies in non-English language texts, conference proceedings, review papers, non-aerobic forms of exercise training, and studies that prescribed cognitive training combined with exercise were excluded. Studies where full text was not available were excluded at the final stage of the screening process. Additionally, studies that included patients with a diagnosis of dementia or AD, cognitively intact older adults or disease populations with comorbid cognitive impairment were excluded from analysis. The quality of studies, as reported in the source papers, was assessed independently using standardised quality assessment tools.

3.3 Results

3.3.1 Identification of studies

Results from the search strategy and selection for review are presented in Figure 3:1. The initial search produced a total of 3834 potentially eligible papers. Studies were filtered into the review by initial screening of titles and abstracts which were independently examined by both reviewers (Kate Devenney (KD), Emer Guinan (EG)). At each stage of the screening and appraisal process, both reviewers met and compared accepted studies and conflicts were resolved using the predefined study inclusion and exclusion criteria as a reference point for discussion. A number of accepted studies (n=26) were identified as conference proceedings or abstracts and excluded as full text was not published and there was no response following authors contacted to gain full text. A total of 52 full-text articles were read and independently assessed for eligibility, of which 12 were included in the final review (Moher et al., 2009) (Figure 3:1).

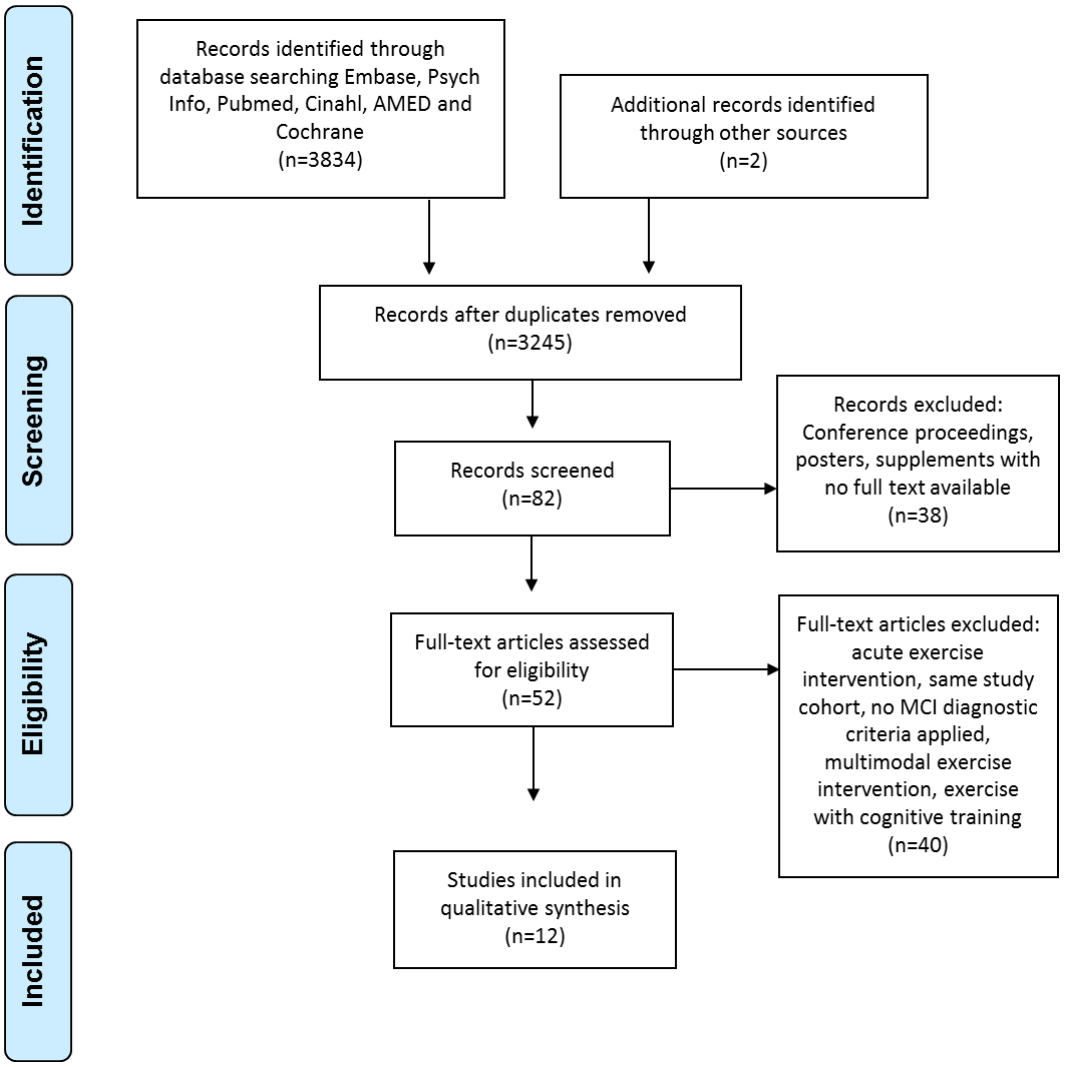

Figure 3:1 PRISMA diagram showing flow of studies into review

3.3.2 Study quality

Two raters (KD, EG) independently evaluated study quality using standardised quality assessment tools. Study quality was assessed using the Cochrane collaboration tool for assessing risk of bias (RCTs) (Higgins et al., 2011) n=8 (Table 3-1) and the Risk Of Bias In Non-randomised Studies of Interventions (Sterne et al., 2016) n=4 (Table 3-2). Overall, the quality of included trials was low to moderate with a number of studies lacking sufficient information to comprehensively assess study quality.

Table 3-1 Risk of bias for RCTs assessed using the Cochrane collaboration risk of bias tool

Study	Sequence generation	Allocation concealment	Blinding of participants, personnel and outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Baker et al. (2010c)	Unclear	Unclear	Low	Low	Low	Low
Gill et al. (2015)	Low	Low	Low	Low	Low	Unclear
Nagamatsu et al. (2013b)	Low	Low	Low	Low	Unclear	Low
Scherder et al. (2005)	Unclear	Unclear	Low	Unclear	Unclear	High
van Uffelen et al. (2008)	Low	Unclear	Low	Low	Low	Low
Varela et al. (2012)	Unclear	Unclear	Unclear	Low	Low	High
Wei and Ji (2014)	Unclear	Unclear	Unclear	Unclear	Low	High
Hu et al. (2014)	Unclear	Unclear	Unclear	Unclear	Low	High

Table 3-2 ROBINS-I: Risk Of Bias In Non-randomised Studies of Interventions

Study	Bias due to confounding	Bias in selection of participants	Bias in classification of interventions	Bias due to deviations from the intended intervention	Bias due to missing data	Bias in measurement of outcome measures	Bias in selection of reported results
De Gobbi Porto et al. (2015)	Moderate	Moderate	Moderate	Low	Serious	Moderate	Serious
Sacco et al. (2015)	Moderate	Low	Low	Low	Low	Low	Moderate
Carson Smith et al. (2013)	Moderate	Low	Low	Low	Serious	Moderate	Low
Tortosa-Martínez et al. (2015)	Moderate	Serious	Low	Low	Low	Low	Low

3.3.3 Study design and subject characteristics

Twelve studies were included for review, with sample sizes ranging from 8 to 198 participants. Study designs included; eight RCTs (Gill et al., 2015, van Uffelen et al., 2008, Varela et al., 2012, Wei and Ji, 2014, Hu et al., 2014, Scherder et al., 2005, Nagamatsu et al., 2013b, Baker et al., 2010c), and four non-randomised studies (Smith et al., 2013a, Tortosa-Martínez et al., 2015, Sacco et al., 2015, De Gobbi Porto et al., 2015). Study participants were diagnosed with MCI according to a wide range of diagnostic criteria. In six studies, MCI was diagnosed according to the Petersen criteria (2004) (Baker et al., 2010c, De Gobbi Porto et al., 2015, Tortosa-Martínez et al., 2015, van Uffelen et al., 2008, Scherder et al., 2005, Sacco et al., 2015). One study applied Albert et al. (2011) MCI diagnostic criteria as study inclusion (Carson Smith et al., 2013). In the remaining studies, a variety of unidimensional MCI diagnostic criteria were described (Table 3-3) (Gill et al., 2015, Nagamatsu et al., 2013b, Varela et al., 2012, Wei and Ji, 2014, Hu et al., 2014).

3.3.4 The effect of exercise on measures of cognitive performance

Due to the heterogeneity of outcome measures used across studies, results are discussed by qualitative synthesis. Study methodologies are described in Table 3-3 along with a summary of interventions and outcomes. Effect sizes and confidence intervals where reported, are included to facilitate comparisons. Exercise intervention is described in accordance with the Frequency, Intensity, Time and Type (FITT) principle to quantify exercise volume.

The Compendium of Neuropsychological Tests: Administration, Norms, and Commentary (Third Edition) was used to categorise cognitive tests into domains of global cognition, memory, executive function, attention and processing speed or visuospatial skills (Strauss et al., 2006). In the results, biological endpoints and CR fitness are discussed separate to the cognitive outcomes.

Table 3-3 Summary of study design, intervention and outcomes of included studies. Exercise interventions described in line with the FITT (frequency, intensity, time and type) principle. HRR=Heart Rate Reserve; SCWT=Stroop Colour Word Task; TMT=Trail Making Test; SDMT=Symbol Digit Modalities Test; BDNF=Brain Derived Neurotrophic Factor; IGF=Insulin Growth Factor; HR= Heart Rate; ADAS-cog=Alzheimer's Disease Assessment Scale-cognitive subscale; MMSE=Mini–Mental State Examination; WMS=Wechsler Memory Scale; ROCF=Rey–Osterrieth Complex Figure; RAVLT=Rey Auditory Verbal Learning Test; WAIS=Wechsler Adult Intelligence Scale; AVLT=Auditory Verbal Learning Test; DSST=Digit Symbol Substitution Test; RPE=Borg Rating of Perceived Exertion; CRT=Choice Reaction Time; SRT=Simple Reaction Time

Author (design)	Participants	Aerobic exercise intervention FITT principle	Cognitive Outcomes	Blood biomarkers	Main results
Baker et al. (2010c) RCT	Amnestic Mild Cognitive Impairment Petersen criteria Aerobic exercise n = 23 versus Stretching and toning control n=10	F: 4 days/week for 6 months I: 75% - 85% HRR T: 45 – 60 min/day T: Aerobic Adherence 93.75%	Memory: Story recall List learning Visual memory Executive function: Verbal fluency SCWT TMT-B Task switching Attention/processing speed: TMT-A SDMT	Insulin Cortisol BDNF IGF-1 B-AMYLOIDS 40 + 42	Significant executive functioning changes (p=0.04) post-intervention (6-months) compared to a stretching and toning control group with favourable effect for women. Increased glucose disposal during the metabolic clamp, reduced fasting plasma BDNF and insulin (women in aerobic exercise) while IGF-1 and BDNF levels increased in exercising men Cortisol levels increased for women in the control group but not for women in the aerobic

					group. For men, cortisol decreased over time for those in the stretching group while remaining stable for the aerobic group (values not reported)
De Gobbi Porto (2015) Non-randomised study	Amnestic and non-amnestic MCI Petersen criteria n=40 No control group	F: 2 days/week for 24 weeks I: Treadmill speed adjusted to maintain HR between ventilator anaerobic threshold and 10% below respiratory compensation point T: increased over first 8 weeks from 30 to 50 minutes duration T: Aerobic treadmill walking Adherence 80%	Global cognition: ADAS-cog MMSE Memory: Visual reproduction and logical memory WMS-R Delayed recall ROCF RAVLT Executive function: TMT-B Stroop test Category and letter fluency Attention/processing speed: TMT-A Visuospatial skills: Clock drawing Block design subtest WAIS ROCF Matrix reasoning		Significant improvement in ADAS-cog as evidenced by a decrease of -2.7 (3.7) points ($p<0.001$), on the ADAS-Cog and also ADAS-cog memory subtest as determined by a decrease of -2.2 (3.1) points ($p<0.001$). Improvements in the delayed visual memory recall (dVMR) subset of the Wechsler Memory Scale-Revised (6.4 ± 12.6, $p=0.003$) and in the Rey-Osterrieth Complex Figure copy (2 ± 5.2, $p=0.02$) within the exercise group
Gill et al. (2015) RCT	<27 MoCA	F:2-3days/week for 26 weeks I: 70-85% max HR T: 60 – 75 minutes	Global cognition: composite score of below cognitive outcomes	Nil	Significant within-group improvements in global cogniton in both the exercise only (0.22 mean standardised change, 95%

	Recruited from existing exercise programme Exercise only n=23 versus Exercise and dual task training n=21	Min 50 classes Max 75 classes T: Largest component is aerobic exercise with some additional strength, balance and flexibility Adherence 78%	Memory: AVLT Executive function: TMT-B Category and letter fluency Attention/processing speed: TMT-A DSST		CI; 0.08 to 0.36) and the exercise plus dual task training arm (0.42 mean standardised change, 95% CI; 0.29 to 0.55) but this was significantly better in the exercise and dual task training arm (0.20 mean standardised change, 95% CI; 0.01-0.39, p=0.04)
Nagamatsu et al. (2013b) RCT	Women with probable MCI <26/30 on the MoCA and subjective memory complaint Aerobic n=30 versus resistance n=28 versus balance and toning n=28	F: 2 days/week for 6 months I:40% HRR and progressed to 70-80% HRR over first 12 weeks RPE 13-15 T: 40 minutes core content and 10 minute warm up and cool-down T: Outdoor walking programme Adherence 60%	Memory: Computerised spatial memory test developed in-house RAVLT Executive function: CRT	Nil	Significant difference is RAVLT loss after interference scores in aerobic group (1.58 ± 1.86) compared to the balance and toning group (2.80 ± 2.58), (p=0.04).
Sacco et al. (2015) Non-randomised study	Petersen criteria n=8 9 month study consisting of two 3-month experimental	F: 2 days/weekly for 3 months I: 60% of HRR and RPE was recorded T: 20 minutes T: Aerobic. Stationary bike	Executive function: Go-no-go inhibition task Attention/processing speed: SRT	Nil	Significant improvements in reaction time during the Go-no-Go task following both interventions with a large effect for the exercise and cognitive enhancement intervention (6 ± 2.4%. 95% CI: -8.2 and -4%;

	interventions separated by a training cessation period of 3 months	Adherence not reported			Cohen's d=0.99) and a medium effect for exercise only (4 ± 2.7%, 95% CI: -6.3 and -1.7%; Cohen's d=0.69)
Carson Smith et al. (2013) Non-randomised study	Albert et al. criteria MCI n=17 versus older adults n=18	F: 4 days/week for 12 weeks I: Gradually increased over the first 4 weeks to 50%-60% of HRR and RPE 15 between weeks 5-12 T: 30 minutes T: Supervised aerobic treadmill training Adherence 96%	Global cognition : MMSE Mattis Dementia Rating Scale-2 Memory: RAVLT WMS III – Logical memory and number sequencing Executive function: Controlled oral word association test Animal fluency Attention/processing speed: SDMT Visuospatial skills: Clock Drawing	Nil	Significant within group changes in memory performance on Trial 1 learning on RAVLT in both patients with MCI (n=17) (pre 3.9 ± 2.1 to post 5.0 ± 2.1) (p=0.006)
Tortosa-Martínez et al. (2015) Non-randomised study	Amnestic MCI Petersen's criteria Exercise n=19 versus usual care n=20	F: 3 days/week for 3 months I: 40% max HR and progressed to 60-75% max HR during the first 4 weeks T: 60 minutes per session	Global cognition: MMSE ADAS-cog Memory: Word list memory (CERAD) Executive function:	Cortisol (neuroendocrine stress system)	Within group analysis showed significant improvement in the exercise group with a 27% improvement in time to complete Trail Making Test-B relative to baseline (pre-intervention 329 ± 190s; post-intervention 239 ± 120s, p=0.046).

		T: Primarily aerobic (walking / bike) with some light strength, balance and flexibility included usually in the warm up and cool down stage Adherence 87%	Verbal fluency TMT-B Attention/processing speed: TMT-A		Intervention group showed peak cortisol 30 min after waking with a significant increase in the drop between peak cortisol and cortisol values at 12pm compared with control group
van Uffelen et al. (2008) RCT	Petersen criteria Group walking moderate intensity + vitamin B supplement or placebo n=77 versus group walking low intensity + vitamin B supplement or placebo n=75	F: 2 days/week for one year I: Moderate intensity group (>three metabolic equivalents). Low intensity group (<three metabolic equivalents) T: One hour T: Aerobic outdoor group walking programme Adherence 63%	Global cognition: MMSE Memory: AVLT Executive function: Verbal fluency SCWT-A Attention/processing speed: DSST	Nil	Nil significant
Varela et al. (2012) RCT	Clinical diagnosis of MCI according to the consensus of the Spanish society of Geriatrics and Gerontology	F: 3 days/week for 3 months I: Low intensity group 40% HRR. Moderate intensity group 60% HRR	Global cognition: MMSE	Nil	Nil significant

	Residential care home residents Group A 40% HRR n=17 versus Group B 60% HRR n=16 versus Group C recreational activities n=15	T: 5 minute warm up and cool down. 20 minutes cycling at target intensity. T: Aerobic. Stationary Bike. Adherence not reported			
Wei and Ji (2014) RCT	MCI participants were selected according to the US mental disorders 4th ed. of the diagnostic and statistical manual in mild neurocognitive standards and the diagnosis standard of shanghai mental health centre Nursing home residents Handball training exercise group	F: 5 days/week for 6 months I: mean intensity 60% max HR T: 30 minutes per day T: Handball training programme was used in the training group Adherence not reported	Global cognition: MMSE	Nil	Significant increases in MMSE scores in the exercise group from baseline (24.33 ± 1.65) to three (25.20 ± 1.24) and six months (25.53 ± 0.82) compared to a sedentary control group (n=30) (baseline 25.00 ± 1.29, three months 24.80 ± 1.35, six months 24.67± 1.42), (p=0.000 for time x group interaction).

	n=30 versus control n=30				
Hu et al. (2014) RCT	MMSE (Chinese version) ≤26 Recruited from community home Exercise n=96 versus control n=102	F: 1 day/week for 6 months I: Not reported T: 90 minutes T: 30 minutes of jogging and 60 minutes of shadow boxing Adherence not reported	Global cognition: MMSE	Nil	Significant improvements in the immediate memory (mean improvement 2.58 ± 0.71, p<0.001) and delayed recall (2.06 ± 1.03, p=0.004) subsections of the MMSE compared to the control group (immediate memory 2.11 ± 0.76 and delayed recall 1.62 ± 1.10)
Scherder et al. (2005) RCT	Petersen criteria Frail nursing home residents Walking group n =15 versus hand/face exercises n=13 versus control n=15	F: 3 days/week for 6 weeks I: Not reported T: 30 minutes T: Aerobic. Slow paced walking. Adherence not reported	Memory: WMS – Revised digit span and verbal learning and memory test Rivermead behavioural memory test Executive function: TMT-B Category naming Attention/processing speed: TMT-A	Nil	Significant improvements in category naming in the slow-paced walking group (22.60 ± 9.68 to 24.80 ± 11.37 number correct answers) and hand/face exercises (24.62 ± 9.26 to 25.69 ± 8.14) compared to the control group (21.60 ± 8.58 to 20.27 ± 9.51) (p=0.03). Effect size in walking group n^2=0.16, large effect size.

3.3.4.1 Exercise and global cognition

Eight studies examined the effect of exercise on global cognition with three studies reporting significant improvement in global cognition (De Gobbi Porto et al., 2015, Gill et al., 2015, Wei and Ji, 2014) with no change in the remaining studies (Varela et al., 2012, Hu et al., 2014, van Uffelen et al., 2008, Tortosa-Martínez et al., 2015, Carson Smith et al., 2013).

Three studies recruited residential care-home residents and measured global cognition using the Mini-Mental State Examination (MMSE). One RCT compared three months, 20 minutes three days/week, of either low (40% HRR) (n=17) or moderate (60% HRR) (n=16) intensity cycling to a control group who completed recreational activities (n=15) (Varela et al., 2012) and found no change in MMSE scores following completion of the low (pre-intervention 19.31 ± 6.12 to post-intervention 20.40 ± 4.15) or moderate intensity intervention (20.56 ± 5.69 to 20.98 ± 5.40), with no between group differences at study completion (p=0.77). In a larger sample of community home residents (n=198), participants completing 90 minutes jogging and shadow boxing once weekly for 6 months, experienced significant improvements in the immediate memory (mean improvement 2.58 ± 0.71, p<0.001) and delayed recall (2.06 ± 1.03, p=0.004) subsections of the MMSE compared to the control group (immediate memory 2.11 ± 0.76 and delayed recall 1.62 ± 1.10). However, between group differences in total MMSE scores were not reported (Hu et al., 2014). In a similar cohort of 30 nursing home residents completing six months of moderate intensity (60% maxHR) handball training, 5 times per week, Wei and Ji (2014) described significant increases in MMSE scores in the exercise group from baseline (24.33 ± 1.65) to three (25.20 ± 1.24) and six months (25.53 ± 0.82) compared to a sedentary control group (n=30) (baseline 25.00 ± 1.29, three months 24.80 ± 1.35, six months 24.67± 1.42), (p=0.000 for time x group interaction).

The remaining studies measured global cognition in community dwelling older people with cognitive impairment. In one single arm intervention (n=40), prescribing twice weekly high intensity exercise for 50 minutes resulted in significant within-group improvements in global cognition, characterised by a decrease of -2.7 (3.7) points (p<0.001), on the Alzheimer's Disease Assessment Scale-Cog (ADAS-Cog) (De Gobbi Porto et al., 2015).

One two armed-RCT recruited participants from an existing exercise programme and compared 26 weeks of moderate intensity (70-85% HRmax) training for 75 minutes, 2-3 times per week in an exercise only group (n=23) to an equivalent exercise protocol in combination with dual task training (n=21) consisting of a square-stepping exercise on a griddled floor mat (Gill et al., 2015). There were significant within-group improvements in global cognitive function (global composite score) in both the exercise only (0.22 mean standardised change, 95% CI; 0.08 to 0.36) and the exercise plus dual task training arm (0.42 mean standardised change, 95% CI; 0.29 to 0.55), but this improvement was significantly better in the exercise and dual task training arm (0.20 mean standardised change, 95% CI; 0.01-0.39, p=0.04).

In a double-blind RCT, Van Uffelen et al. (2008) used a two-by-two factorial design to compare the effects of a year-long moderate intensity (>3 metabolic equivalent (METs)) exercise programme completed twice per week for one hour (n=77) to a low intensity protocol (<3 METs) (n=75), with participants in both arms randomised to receive daily vitamin B supplementation or placebo supplements. Global cognitive scores did not change in either exercise arm. In two non-randomised trials prescribing three months of moderate or high intensity exercise compared to an inactive usual care or active healthy control group found no change in measures of global cognition on the MMSE or ADAS-cog (Tortosa-Martínez et al., 2015, Carson Smith et al., 2013).

3.3.4.2 Exercise and memory

Eight studies measured memory performance with four studies prescribing three or six-months of aerobic exercise training reporting significant improvement in a task of memory performance (De Gobbi Porto et al., 2015, Gill et al., 2015, Nagamatsu et al., 2013b, Carson Smith et al., 2013), with no significant improvements reported in the remaining studies (Baker et al., 2010c, van Uffelen et al., 2008, Scherder et al., 2005, Tortosa-Martínez et al., 2015).

In addition to the global cognitive improvement reported by De Gobbi Porto et al. (2015), a significant improvement in the ADAS-cog memory subtest as determined by a decrease of -2.2 (3.1) points ($p<0.001$) was also reported following six months high intensity exercise. Furthermore, there were improvements in the delayed visual memory recall subset of the Wechsler Memory Scale-Revised (WMS-R) (6.4 ± 12.6, $p=0.003$) and in the Rey-Osterrieth Complex Figure (ROCF) copy (2 ± 5.2, $p=0.02$) within the exercise group.

A number of studies reported changes in verbal learning and memory tasks. A three-armed RCT, involving 86 women who completed either six months moderate intensity exercise (70%-80% Heart Rate Reserve (HRR)), twice weekly for 40 minutes, an equivalent schedule of balance and toning exercise or a resistance exercise training schedule reported improved performance on the RAVLT (lower loss after interference) (1.58 ± 1.86) in the aerobic group compared to the balance and toning group (2.80 ± 2.58), (p=0.04). (Nagamatsu et al., 2013b). In a group of older adults attending a community based exercise class, Gill et al. (2015) described significant between group differences in verbal learning and memory composite scores (0.30, 95% CI: 0.04 – 0.56, p=0.02) following 26 weeks of moderate intensity exercise plus dual task training group (n=21) (0.68, 95% CI: 0.50-0.86) compared to the exercise only group (n=23) (0.38, 95% CI: 0.18-0.58). Smith et al. (2013) reported significant within group changes in memory performance on Trial 1 of a list-learning task on RAVLT in both patients with MCI (n=17) (pre 3.9 ± 2.1 to post 5.0 ± 2.1) and older adults without cognitive impairment (n=18) (pre 5.4 ± 1.9 to post 6.3 ± 1.5) following 12 weeks of moderate intensity (60% HRR) exercise, completed for 30 minutes, 4 days per week.

In contrast, three RCTs (Baker et al., 2010c, van Uffelen et al., 2008, Scherder et al., 2005) and one non-randomised study (Tortosa-Martínez et al., 2015), found no change in memory performance with exercise training. These studies prescribed a range of exercise intensity and intervention durations including a six week slow paced walking programme in a group of frail nursing home residents (Scherder et al., 2005), a one year low and moderate intensity walking programme (van Uffelen et al., 2008), a six month high intensity exercise intervention (Baker et al., 2010c) and three months of moderate intensity training (Tortosa-Martínez et al., 2015). Measures of memory performance included word list learning, AVLT, word list memory on the ADAS-cog, story recall, visual memory and components of the WMS.

3.3.4.3 Exercise and executive function

Nine studies included a measure of executive function with five of the nine studies reviewed reporting significant improvements in executive function with exercise training (Scherder et al., 2005, Tortosa-Martínez et al., 2015, Sacco et al., 2015, Baker et al., 2010c, Gill et al., 2015) and no significant change within other studies (van Uffelen et al., 2008, Nagamatsu et al., 2013b, Carson Smith et al., 2013, De Gobbi Porto et al., 2015).

In one non-randomised study, Tortosa-Martínez et al. (2015) assigned a group of 39 people with amnestic MCI to either 60 minutes moderate intensity (60-75% HRmax) exercise performed twice weekly, or to usual care. Within group analysis showed significant improvements in executive function in the exercise group with a 27% improvement in time to complete Trail Making Test-B (TMT-B) relative to baseline (pre-intervention 329 ± 190s; post-intervention 239 ± 120s, p=0.046).

In a small group (n=8) of people with MCI, a 9-month crossover study consisting of two separate three-month interventions of aerobic exercise prescribed for three months at a moderate intensity (60% HRR), twice weekly for 20 minutes, or the equivalent exercise prescription plus cognitive enrichment computer-based cognitive tasks performed while cycling, significant improvements were observed in reaction time during the Go-no-Go task following both interventions with a large effect for the exercise and cognitive enhancement intervention (6 ± 2.4%. 95% CI: -8.2 and -4%) and a medium effect for exercise only (4 ± 2.7%, 95% CI: -6.3 and -1.7%) (Sacco et al., 2015).

Three RCTs reported significant changes in executive function. One RCT reported significant improvements in a group of nursing home residents in category naming following six weeks of trice weekly slow-paced walking (22.60 ± 9.68 to 24.80 ± 11.37 number correct answers) and hand/face exercises (24.62 ± 9.26 to 25.69 ± 8.14) compared to the control group (21.60 ± 8.58 to 20.27 ± 9.51) (p=0.03). Similarly, verbal fluency composite scores, reported as a sub analysis of individual cognitive domains within the global cognitive composite score, significantly improved following 26 weeks of moderate intensity exercise and dual task training (0.60, 95% CI: 0.32-0.87) compared to exercise only (-0.03, 95% CI: -0.33 – 0.27) (p=0.003) (Gill et al., 2015). In a six-month moderate to high intensity (75-85% HRR) aerobic exercise protocol in people with MCI, the intervention arm had significantly better executive functioning scores (verbal fluency, stroop, TMT-B and task switching) (p=0.04) post-intervention compared to a stretching and toning control group (values not reported). A significant interaction effect was identified with gender, suggesting a favourable treatment effect for women.

Four studies reviewed reported no change in measures of executive function with aerobic exercise training (De Gobbi Porto et al., 2015, Nagamatsu et al., 2013a, Carson Smith et al., 2013, van Uffelen et al., 2008). These included a non-randomised experimental study of moderate intensity 12-week duration (Carson Smith et al., 2013), one RCT and one single arm intervention that both prescribed moderate-high intensity exercise for a six-month period (Nagamatsu et al., 2013b, De Gobbi Porto et al., 2015), and a yearlong

RCT of low and moderate intensity walking (van Uffelen et al., 2008). Trail Making Test-B, Stroop, category fluency, verbal fluency, controlled oral word association test or choice reaction time did not demonstrate any measureable change.

3.3.4.4 Exercise and attention and processing speed

Eight studies measured attention and processing speed; four RCTs and four non-randomised studies (Baker et al., 2010c, De Gobbi Porto et al., 2015, Gill et al., 2015, Sacco et al., 2015, Carson Smith et al., 2013, Tortosa-Martínez et al., 2015, van Uffelen et al., 2008, Scherder et al., 2005) with only one study reporting significant changes (Baker et al., 2010c).

Baker et al. (2010) reported significant between group differences in attention and processing speed (symbol-digit modalities) following a six-month high intensity exercise programme in comparison with a stretching and toning protocol (values not reported). In contrast, two studies also prescribing a six-month moderate-high intensity exercise intervention reported no change in measures of attention and processing speed as measured on Trail Making Test-A or Digit-Symbol Substitution test (De Gobbi Porto et al., 2015, Gill et al., 2015). A further three non-randomised studies prescribing three months of moderate intensity exercise, reported no changes in measures of attention or processing speed on a simple reaction time, symbol digit modalities and TMT-A test (Sacco et al., 2015, Carson Smith et al., 2013, Tortosa-Martínez et al., 2015). A six-week intervention of slow walking in a group of frail nursing home residents did not produce any significant changes on Trail Making Test-A performance (Scherder et al., 2005).

3.3.4.5 Exercise and visuospatial skills

Two non-randomised studies measured the influence of three and six months of moderate-high intensity exercise training on visuospatial skills (De Gobbi Porto et al., 2015, Carson Smith et al., 2013) with neither study reporting significant changes in response to exercise training.

3.3.5 Biomarkers

Two studies included a biomarker measurement relative to cognitive function. One RCT, a six-month moderate to high intensity (75-85% HRR) aerobic exercise protocol reported sex differences in biomarker response to exercise, despite comparable gains in CR fitness (Baker et al., 2010c). For women, increased glucose disposal during the

metabolic clamp, and reduced fasting plasma levels of insulin, cortisol, and brain-derived neurotrophic factor were observed following the six months of aerobic training. A sex-specific effect of aerobic exercise vs stretching was observed for plasma BDNF with a higher BDNF response observed in males. For men, aerobic exercise also increased plasma levels of insulin like growth factor-1 (absolute values not reported) (Baker et al., 2010c). In a non-randomised study, Tortosa-Martínez et al. (2015) assigned a group of 39 people with amnestic MCI to either 60 minutes moderate intensity (60-75% HRmax) exercise performed twice weekly, or to usual care. Significant increases in the peak of cortisol (30 min after waking – sample two) and the cortisol values at 12:00 hours (sample three) was observed in the exercise group compared to the control group (p=0.02) (values not reported).

3.3.6 Cardiorespiratory fitness

In the twelve studies included in this review, six studies measured baseline and post intervention cardiorespiratory (CR) fitness with a submaximal (n=3) or maximal exercise (n=3) test (Tortosa-Martínez et al., 2015, Baker et al., 2010c, De Gobbi Porto et al., 2015, Nagamatsu et al., 2013b, Carson Smith et al., 2013, Gill et al., 2015) (Table 3-4). Three studies reported significant gains in CR fitness (VO_2max), two after a high intensity 6-month intervention (Baker et al., 2010c, De Gobbi Porto et al., 2015) and one study after 12 weeks of moderate intensity exercise (Carson Smith et al., 2013). All three studies that reported significant change in VO_2max reported significant change in cognitive performance in measures of executive function (Baker et al., 2010c), global cognition (particularly memory) (De Gobbi Porto et al., 2015) and episodic memory (verbal list learning) (Smith et al., 2013a). The other three studies that measured CR fitness failed to accurately report post intervention values to allow interpretation (Gill et al., 2015, Nagamatsu et al., 2013b, Tortosa-Martínez et al., 2015). The remaining six studies in this review did not include a measure of CR fitness.

Table 3-4 Studies that included an objective measurement of cardiorespiratory fitness pre-post structured aerobic exercise intervention

Study	Exercise test	Results
Baker et al. (2010c)	Modified Balke maximal graded treadmill test	Baseline VO_2peak (ml/kg/min) Aerobic group: Women 22.6 (4.2) Men 25.2 (5.4) Stretching and toning group: Women 20.4 (1.9) Men 23.6 (5.9) Post intervention + 11% increase in VO_2 peak reported in the aerobic training group and –7% in the stretching and toning group (p=0.003). Absolute values not reported.
Carson Smith et al. (2013)	Modified Balke-Ware protocol submaximal treadmill test	VO_2peak (ml/kg/min) MCI: pre 19.1 (4.1) post 21.5 (3.4) Control (cognitively intact group): pre 20.1 (5.0) post 21.2 (4.1) Both groups received the same exercise intervention. Within group difference, significant mean increase in VO_2peak (p=0.004)
De Gobbi Porto et al. (2015)	Treadmill VO_2max test Increased increments in velocity and inclination every minute until exhaustion	VO_2max (ml/kg/min) Baseline: 22.0 (3.5) Post intervention: 23.8 (4.0) Within group difference 1.8 (2.0), (p=<0.001)
Nagamatsu et al. (2013b)	Six minute walk test (submaximal)	Values not reported
Gill et al. (2015)	The step test (submaximal)	Baseline predicted VO_2max (ml/kg/min) Exercise only: 27.6 (10.3) Exercise and dual task training: 27.8 (8.6) Post intervention values not given. Improved fitness was not anticipated as both intervention groups were actively exercising prior to study enrolment.
Tortosa-Martínez et al. (2015)	Six minute walk test (submaximal)	Distance (metres) on six minute walk test Exercise group: Baseline 431.84 (56.79) Post intervention 493.88 (31.22) Control group: Baseline 401.05 (109.77)

		Post intervention (399.66 (87.00) Significant between group differences (p=0.000). Predicted VO_2max not estimated.

3.4 Discussion

This review summarises evidence from exercise intervention studies examining the effect of structured aerobic exercise on cognitive performance in people with MCI. Evidence pertaining to biomarkers relative to cognition and CR fitness is also summarised. This systematic review found low to moderate quality evidence to support the effectiveness of aerobic exercise interventions in improving cognitive function in people with MCI. Furthermore, the results reveal a paucity of exercise trials in MCI populations examining CR fitness and biological mechanisms that may underpin the relationship between aerobic exercise and cognitive performance. While available evidence is generally inconsistent and of variable quality, some tentative conclusions can be drawn from the results. Under certain aerobic exercise prescription parameters; global cognition, memory and executive function appear malleable to exercise induced cognitive change in people with MCI. In contrast, measurements of attention, processing speed or visuospatial skills did not demonstrate any significant change with aerobic exercise training.

The recent update to the AAN practice guideline on MCI recommends people with MCI participate in twice weekly exercise. While previous research has highlighted a positive relationship between aerobic fitness, brain health, and cognitive performance in adults without cognitive impairment (Kramer et al., 2000, Kirk-Sanchez and McGough, 2014), the dose-response relationship between aerobic exercise and cognition remains poorly understood in individuals with MCI. A summary of the results in this current review indicate a moderate-high intensity aerobic prescription of ≥6 month duration at a minimum is necessary to produce a change in cognitive performance in global cognition, memory and executive function (Baker et al., 2010c, De Gobbi Porto et al., 2015, Gill et al., 2015, Nagamatsu et al., 2013b, Wei and Ji, 2014, Hu et al., 2014).

With the exception of the study by Smith et al. (2013), most studies reporting changes in global cognition, memory and executive function prescribed a moderate to high intensity intervention of six month duration (van Uffelen et al., 2008, Nagamatsu et al., 2013b, Gill et al., 2015, Hu et al., 2014, Wei and Ji, 2014, De Gobbi Porto et al., 2015, Baker et al., 2010c) with executive function also demonstrating change following shorter duration

interventions (six weeks to three months) across a range of exercise intensities (Scherder et al., 2005, Tortosa-Martínez et al., 2015, Sacco et al., 2015). It can be postulated that low intensity aerobic exercise is not sufficient to elicit the neurotrophic and neuroplastic changes that augment cognitive performance. Within a subset of memory performance, episodic memory measured using verbal learning and memory tasks significantly improved across three studies (Carson Smith et al., 2013, Nagamatsu et al., 2013b, Gill et al., 2015), which may represent the preservation of hippocampal volumes through trophic induced neurogenesis that has been shown to occur in response to aerobic exercise in healthy older adults (Cotman et al., 2007).

Two studies that included a biological marker reported improved cortisol profiles following participation in a moderate - high intensity aerobic exercise training which was associated with improved performance on measures of executive function (Baker et al., 2010c, Tortosa-Martínez et al., 2015). Previous studies have shown that elevated levels of cortisol are an established risk factor for cognitive dysfunction and decline in cognitive ageing (Lee et al., 2007, Lucassen et al., 2014). Moreover, the deleterious effects of highly elevated basal cortisol levels have been associated with cognitive impairment, neuro-structural changes and decreased hippocampal volume in people with AD (O'Brien et al., 1996, Lupien et al., 1998). Several observational studies of non-demented older adults have linked increased basal cortisol levels with decreased cognitive abilities in hippocampus-dependent learning and memory and reduced hippocampal volume (Pruessner et al., 2005). Stawski et al. (2011) reported that higher cognitive functioning in adults, particularly executive function was associated with healthier daily cortisol profiles including a steeper diurnal cortisol slope, higher morning cortisol levels, and lower afternoon and evening cortisol levels. However, the circadian pattern of cortisol secretion is complex and further studies are required to establish exercise-induced changes in the circadian pattern of cortisol secretion and the interaction between cortisol patterns and cognitive function.

In a recent study, CR fitness did not differ significantly between an amnestic MCI group compared to an amnestic MCI group (Ding et al., 2018). However, CR fitness has demonstrated a modest reduction in subjects with AD (34.7 ± 5.0 mL/kg/min) compared to cognitive normal older adults (38.1 ± 6.3 mL/kg/min, $p = 0.002$) (Burns et al., 2008). CR fitness is considered a modifiable risk factor for cognitive decline and results in this review indicate that CR fitness is amenable to 3-6 months moderate–high intensity structured aerobic exercise intervention in MCI cohorts (Baker et al., 2010c, De Gobbi Porto et al., 2015, Smith et al., 2013a). As one of the fundamental goals of aerobic

training is to improve cardiorespiratory fitness, future studies should measure CR fitness as a key outcome to ascertain the effectiveness of the intervention.

Overall trials reviewed were of a low to moderate quality and presented with a number of methodological limitations that warrant further discussion. Firstly, it was difficult to assess the clinical significance of findings as a number of studies reporting cognitive change failed to provide estimates of appropriate effect sizes and confidence intervals, which should be reported as a minimum expectation (American Psychology Association, 2009). In addition, a huge variety of cognitive tasks were used with results measured, analysed and reported in many different ways and studies failed to provide any theoretical justification for the selection of cognitive tasks. It was unclear in the current review whether studies were not sufficiently powered to see significant changes or results represented of a lack of effectiveness. A number of studies included were not powered on a primary outcome and presented a high risk of type 1 error due to running multiple statistical analysis without sufficient power. Future studies should ensure sufficient power with a power calculation based on the studies primary outcome, and use a standardised approach to the reporting of cognitive outcomes to provide more comparability of results. Studies that reported improvements in global cognition, memory of executive function presented with a number of methodological issues including recruitment from nursing home populations of older persons with MCI (Wei and Ji, 2014, Scherder et al., 2005), recruitment from an existing exercise programme (Gill et al., 2015), small sample size (Sacco et al., 2015) and absence of an inactive control group (De Gobbi Porto et al., 2015, Carson Smith et al., 2013).

Secondly, participant selection was biased across a number of studies with four studies (Varela et al., 2012, Hu et al., 2014, Wei and Ji, 2014, Scherder et al., 2005) exclusively recruiting participants who were nursing home care residents and therefore the generalisability of the results to the general MCI population is limited. Furthermore, MCI diagnostic criteria varied across studies with seven different MCI diagnostic criteria applied which presents the issue of a heterogeneous MCI sample. Three studies sub classified by MCI type (amnestic and non-amnestic MCI) (Baker et al., 2010c, De Gobbi Porto et al., 2015, Tortosa-Martínez et al., 2015). Amnestic MCI and non-amnestic MCI separation is not only theoretical but supported by observed differences in both structural imaging and neuropsychological tests (Csukly et al., 2016). As people with amnestic MCI have a higher suspicion of an underlying neurodegenerative process and are known to have a higher rate of conversion to AD (Petersen et al., 1999), refinement of MCI subtypes in intervention studies and recruiting a homogenous patient cohort using

standardised criteria may help to predict the direction of progression and create a more targeted exercise intervention (Devenney et al., 2017). The NeuroExercise trial, to which all studies within this thesis are closely aligned will address many of the questions and methodological concerns highlighted in this review.

3.5 Conclusion

The evidence to support aerobic exercise training in an MCI population is limited and most studies show only modest or partial benefits. However, there is a small body of emerging evidence that aerobic exercise of moderate intensity performed for six months has the capacity to improve cognitive performance in areas of global cognition, memory and executive function in people with MCI in people with MCI. Attention, processing speed or visuospatial skills did not appear amenable to exercise induced change. Further high-quality studies are needed in this patient population to gain greater understanding of the optimal training regimen for this patient cohort. Future research should focus on harmonisation of cognitive tests utilised, reliably report exercise prescription and adherence and include objective measures of CR fitness to assess intervention effectiveness. Examination of the underlying biological processes that mediate this relationship also requires further research.

4 Chapter 4: Study I: High intensity acute aerobic exercise increases brain derived neurotrophic factor in mild cognitive impairment: a randomised controlled study

4.1 Introduction

A significant body of work has investigated the effects of acute exercise (defined as a single bout of exercise) on cognition. Meta-analytic reviews report an overall small positive effect of acute exercise on cognitive performance (Effect Size (ES) = 0.10), especially in areas of prefrontal cortex-dependent cognition (Chang et al., 2012, Lambourne and Tomporowski, 2010, McMorris and Hale, 2012). Studies in both animal models and human subjects have described a number of neurophysiological and neurochemical changes after an acute bout of exercise (Basso and Suzuki, 2017). While the exact neuronal mechanisms underlying the acute exercise-cognitive relationship have not been fully elucidated, recent evidence in healthy cohorts postulates Brain Derived Neurotrophic Factor (BDNF) as a mediator of this relationship (Piepmeier and Etnier, 2015). A single session of exercise has been shown to increase concentrations of peripheral BDNF in a transient and intensity-dependent manner in healthy populations (Schmidt-Kassow et al., 2014, Ferris et al., 2007, Tang et al., 2008, Saucedo Marquez et al., 2015, Schmolesky et al., 2013, Knaepen et al., 2010).

The transitional phase of MCI along the cognitive continuum presents an opportunity for targeted interventions such as the exercise-induced upregulation of BDNF. As chronic exercise is the cumulative result of regular bouts of acute exercise, understanding the acute effects of exercise is an integral part of building a comprehensive understanding of the long-term effects of exercise on cognitive function (Basso and Suzuki, 2017). Investigating the neurobiological changes that may modulate these acute effects over time, will help in deepening the understanding of the long-term structural and physiological changes that have been described following long-term exercise interventions and may also help to determine optimal strategies to maximise the effects of both acute and chronic exercise on brain functioning in individuals with MCI.

4.2 Aims and objectives

The aim of this study was to examine the effect of a short bout of high intensity aerobic exercise on serum BDNF (sBDNF) concentration and cognitive performance in individuals with MCI. The working hypothesis was that a short bout of high intensity

exercise would significantly increase sBDNF and cognitive performance compared to a resting control condition. The specific objectives were:

- To investigate the immediate change in sBDNF and cognitive performance following a short bout of high intensity aerobic exercise compared to a resting control condition
- To explore sex differences in sBDNF and cognitive performance following an acute bout of high intensity exercise

4.3 Methods

4.3.1 Study design

Study I was conducted during the baseline assessment for the NeuroExercise study. Participants were randomised using a computer generated randomisation list to one of two testing schedules. Group A represented the exercise condition while group B was designed to act as the control condition. Outcome measurements were collected at T1 (baseline), T2 (post the exercise condition in group A and post a resting control condition for group B) with T3 measurements (post exercise) only collected in group B.

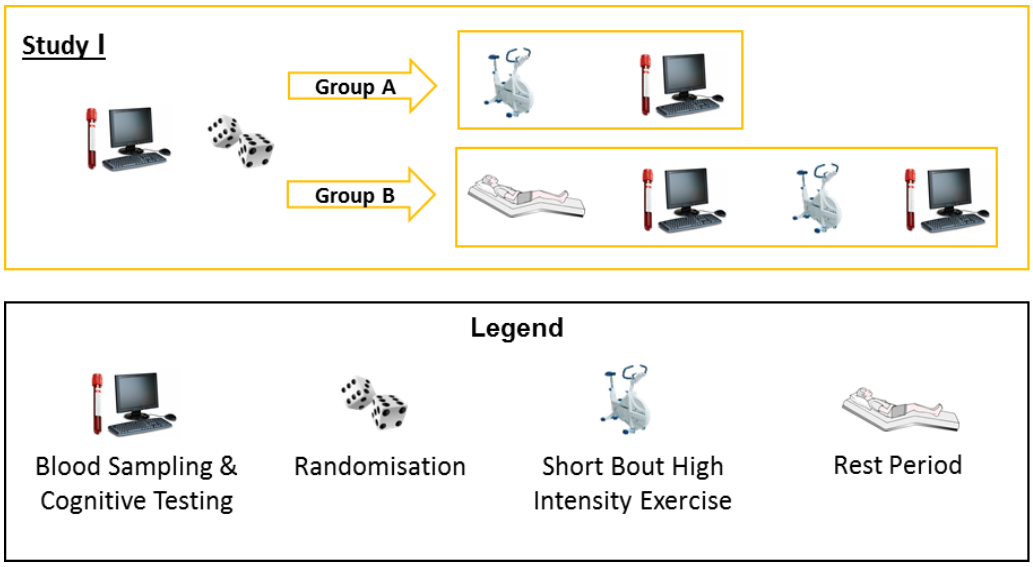

Figure 4:1 Study design and schedule of outcome assessments in Study I

4.3.2 Participants

4.3.2.1 Inclusion and exclusion criteria

Full details of the study recruitment, diagnostic, inclusion and exclusion criteria are available in Chapter 2, Section 2.3.2 – 2.3.5.

4.3.3 Study outcomes

4.3.4 Blood sampling for BDNF measurement

A pre-exercise resting blood sample was collected prior to administration of cognitive measures. The post-exercise blood sample was collected between 0-10 minutes following the exercise or control condition. Details on blood sampling technique and laboratory analysis are available in Chapter 2, Section 2.5.1 - 2.5.3.

4.3.5 Cognitive performance

A battery of cognitive tests were performed following each blood draw. These included:

1. CANTAB Paired Associate Learning (PAL) task, a measure of visuospatial learning and memory.
2. Sustained Attention to Response Task (SART), a computerised Go-No-Go paradigm measuring sustained attention
3. Stroop Neuropsychological Screening Test (Stroop) measuring executive function

Testing took approximately 30 minutes to complete. Full details on the psychometric properties and the standardised administration of each cognitive test is outlined in Chapter 2, Section 2.5.5 – 2.5.8.

4.3.6 Intervention

Participants performed a graded cardiopulmonary exercise test to volitional exhaustion as per WHO protocol (Fletcher et al., 2001). This intervention was complete as described in Chapter 2.4.1.

4.3.7 Sample size

A recent meta-analytic review reported that an acute bout of exercise increased BDNF levels with a moderate effect size (Hedges' g = 0.46, SE = 0.08, 95% CI = 0.29–0.62, z = 5.49, p < 0.001) (Szuhany et al., 2015). Using these values, with 0.05 significance level and 80% power, 32 participants were required per arm to demonstrate an effect size of 0.46 in people with MCI.

4.3.8 Statistical analysis

SPSS 24 (SPSS Inc; Chicago, IL, USA) was used for analysis with statistical significance set at $p<0.05$. Kolmogorov-Smirnov test ($p>.05$) and visual inspection of histogram and

Q-Q plots was used to assess assumptions of normality on all independent baseline variables. In the case of non-normally distributed data, non-parametric tests were performed.

To standardise and avoid skewing data, BDNF data were examined for outliers, with measurements ±2 SDs removed from the mean excluded as per standard approach (Griffin et al., 2011). Following these criteria, n=9 were removed from further analysis.

For the primary analysis, between-group differences between T1 and T2 were analysed for all study variables using an Independent samples t-test for normally distributed data and using a Mann-Whitney U Test for non-normally distributed data. In the secondary analysis, Friedman's Test and ANOVA was used to measure the change over time in study outcomes in group B. Wilcoxon Signed Rank Tests and Paired Sample T-Tests were performed in post-hoc analysis to determine effect size and compare T1–T2 ,T2-T3 and T1-T3 in group B. As secondary analysis involved multiple comparisons, a Bonferroni correction was applied and alpha level was revised to 0.025.

4.4 Results

Participants were enrolled from February 25th, 2016 and data collection for this study ended on July 17th, 2017. 64 participants were enrolled and randomised to either group A (n=35) or group B (n=29).

4.4.1 Participant characteristics

Participant characteristics (age, sex, education, MoCA and Body Mass Index (BMI)) were similar between groups at baseline (Table 4-1). Participants had a mean age of 70.5 years (± 6.3), 53.2% female, mean MoCA score of 22.0 (± 2.5) and the majority (n=38, 59.4%) were highly educated (>13 years). Cardiorespiratory (CR) fitness levels categorised based on age and gender norms revealed a large proportion (n=54, 84.4%) were categorised as very poor (<20th percentile) (ACSM, 2013). Despite randomisation, baseline CR fitness was significantly higher in group B (20.34 ± 6.47 mL/kg/min) compared to group A (17.56 ± 4.14 mL/kg/min).

Table 4-1 Baseline participant characteristics Study IV. Data are presented as mean ± SD for normally distributed data and as median ± IQR for non-normally distributed data. Note statistical significance; *$p < .05$

Variable	Group A: Exercise n=35	Group B: Control n=29	p-value
Gender (M/F)	13/22	17/12	0.14
Age (years)	71.7 (5.3)	69.0 (7.2)	0.09
Education (years)	12.5 (3.0)	14.0 (3.2)	0.07
MoCA	21.6 (2.5)	22.4 (2.6)	0.24
BMI (kg/m2)	27.44 (4.49)	26.14 (4.21)	0.23
VO_2max (mL/kg/min)	17.56 (4.14)	20.34 (6.47)	*0.002

There were no significant between group differences in baseline measures of cognitive performance or sBDNF concentration. Baseline sBDNF did not correlate with MoCA (rho=.10, p=.46), PAL task (rho=.10, p=.44), age (rho= -.02, p=.87) or CR fitness (VO_2 max) (rho=-.01, p=.92). Baseline sBDNF concentration for male (3699.52 ± 6758.59 pg·ml^{-1}) and female (5058.11 ± 6280.08 pg·ml^{-1}) participants were comparable (p=.22). Exercise duration and intensity did not differ between group A and group B (Table 4-2).

Table 4-2 Objective measurements of exercise intensity and duration during performance of the exercise condition (short bout high intensity) in group A and group B. Data are presented as mean ± SD.

	Group A n=35	Group B n=29	p-value
Time (minutes:seconds)	9:11 (3:63)	10:25 (2:26)	0.11
Max watts ($Watts_{max}$)	100 (50)	100 (50)	0.34
Max HR (HR_{max})	118 (20)	124 (21)	0.27
Peak lactate (mmol/L)	5.0 (4.8)	4.4 (2.7)	0.16
Lactate change (mmol/L)	2.9 (3.5)	2.8 (3.5)	0.33
Respiratory Exchange Ratio (RER)	1.06 (0.12)	1.06 (0.07)	0.95

Table 4-3 Effect of intervention (exercise v control) on BDNF and cognitive outcomes. Data are presented for the exercise (group A) and control group (group B) as mean ± SD for normally distributed data and as median ± IQR for non-normally distributed data. Note p-value represents within group differences with statistical significance; *p < .05. BDNF: Brain Derived Neurotrophic Factor. PALTEA: Paired Associate Learning Total Errors Adjusted. CWS: Colour Word Score. SART: Sustained Attention to Response Task. CE: Commission Errors. RT: Reaction Time.

Variables		Baseline T1	Follow-up T2	Difference within groups	p-value	Effect size
BDNF pg·ml^{-1}						
	Exercise	4642.51 (7065.08)	5308.17 (6355.73)	123.96 (2690.97)	0.07	n/a
	Control	5330.86 (10346.65)	4477.95 (5002.88)	-530.79 (1427.44)		
BDNF pg·ml^{-1}outliers excluded						
	Exercise	4564.61 (5737.23)	5173.27 (5997.54)	135.86 (1709.74)	*0.02	0.3
	Control	4593.74 (9558.29)	3974.66 (3668.22)	-530.79 (838.43)		
PALTEA						
	Exercise	44 (30)	46 (23)	.26 (10.29)	0.08	n/a
	Control	44 (22)	33 (29)	-6 (15.3)		
Stroop CWS						
	Exercise	66.42 (28.51)	70.48 (30.66)	4.00 (16.00)	0.45	n/a
	Control	75.25 (26.97)	77.93 (27.42)	1.00 (13.00)		
SART CE						
	Exercise	2.5 (5)	4 (4)	-0.5 (5)	*0.02	0.28
	Control	3 (4)	2 (3)	1 (3)		
SART RT (ms)						
	Exercise	142.04 (83.50)	128.07 (74.42)	4.84 (39.24)	0.055	n/a
	Control	154.57 (78.90)	123.61 (79.62)	27.66 (51.36)		

4.4.2 Primary analysis: between group difference in BDNF and cognitive performance

sBDNF concentration increased in group A (exercise condition) from T1 (4564.61 ± 5737.23 pg·ml^{-1}) to T2 (5173.27 ± 5997.54 pg·ml^{-1}) and decreased in group B (resting control condition) from T1 (4593.74 ± 9558.29 pg·ml^{-1}) to T2 (3974.66 ± 3668.22 pg·ml^{-1}), indicating a medium effect size (p=0.024, ES =.3), (Figure 4:2). The median % relative change in sBDNF concentration from T1 to T2 in response to exercise in group A was 7.07% (± 31.30%) and -13.3% (± 22.49%) in response to a resting control condition in group B (p=0.06).

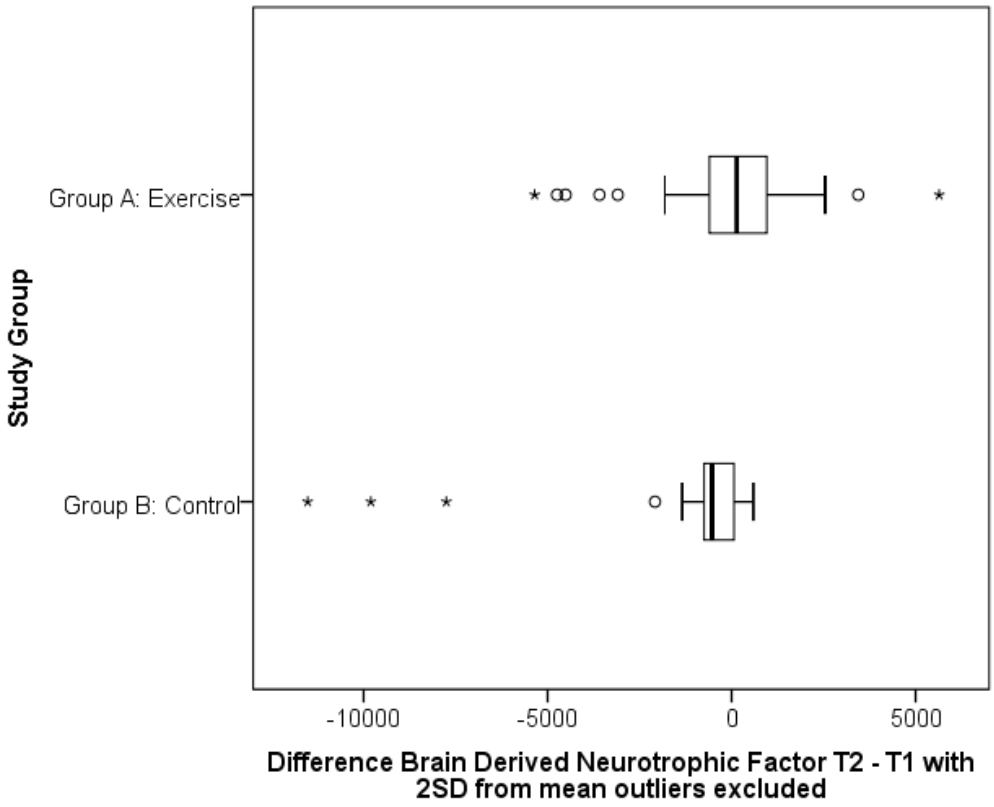

Figure 4:2 Boxplot showing the change in serum BDNF in response to a high intensity exercise or resting control condition

SART commission error rate increased in group A (Md -.50, n=34) and decreased in group B (Md 1.0, n=29) from T1 to T2, U=654.000, z=2.240, r=0.28 representing a small effect size. An acute bout of high intensity exercise did not significantly alter PALTEA, Stroop CWS or SART RT (Table 4-3).

4.4.3 Secondary analysis: change over time within group B

Repeated measures analysis within group B indicated a statistically significant difference in sBDNF concentration across the three timepoints (p = 0.005). Serum BDNF concentration reduced significantly during the resting condition between T1 (Md=4043.97 ± 3982.81 pg·ml^{-1}) and T2 (Md=3076.75 ± 2800.29 pg·ml^{-1}), p = 0.01, with a medium effect size (r=.38), and increased significantly from T2 (Md=3076.75 ± 2800.29 pg·ml^{-1}) to T3 following completion of a short bout of high intensity aerobic exercise (Md=3605.68 ± 5201.05 pg·ml^{-1}), p = 0.001, with a medium to large effect size (r=.48) (Table 4-4). The relative change in sBDNF is consistent with the findings of the primary analysis, with the mean % relative change in sBDNF concentration from T2 to T3 (post exercise) in group B of 15.7% (± 22.1%).

Stroop CWS (Wilk's Lambda =.668, F (2,26)=6.461, p=.005, multipartial eta squared =.33) and SART reaction time (2, n=29) = 0.036 p = 0.005) changed significantly over time within Group B, indicating improved cognitive performance. There were significant increases in Stroop CWS following participation in the exercise condition with improved Stroop CWS from T1 (M = 75.25 ± 26.97) to T3 (M = 83.93 ± 21.47) (mean increase = -8.679, 95% confidence interval -13.55 to -3.80), (p=0.001, ES .34). Furthermore, SART reaction time reduced significantly from T1 (Md 154.57 ms ± 78.90) to T2 (Md 123.61 ms ± 79.62), (p=0.004, ES 0.37), with no significant change in SART commission errors within Group B. Additionally, PALTEA did not change significantly over time (2, n=29) = 7.000. p = 0.03) although a non-significant decrease in error rate was observed from from T1 (Md 44 ± 22) to T2 (Md 33 ± 29), (z=-2.130, p=0.03, ES 0.27) and from T1 to T3 (Md=28 ±) (z=-2.232, p=.026, ES 0.29) (Table 4-4).

Table 4-4 Secondary analysis measuring change over time in study outcomes within group B.

Bonferroni correction applied and alpha level $p < 0.025$.

Variables	Baseline T1	Post control condition T2	Post exercise condition T3	p-value
BDNF pg·ml^{-1} outliers excluded	4593.74 (9558.29)	3974.66 (3668.22)	4790.90 (6713.17)	0.005*
Cantab PALTEA	44 (22)	33 (29)	28 (30)	0.03
Stroop CWS	75.25 (26.97)	77.93 (27.42)	83.93 (21.47)	0.005*
SART CE	3 (4)	2 (3)	2 (3)	0.25
SART RT (ms)	154.57 (78.90)	123.61 (79.62)	142.07 (65.87)	0.005*

4.4.4 Sex differences in acute exercise BDNF and cognitive response

There was a significant difference in SART RT pre to post exercise in female participants (Pre Md 156.14ms ± 83.31 to post Md 134.62ms ± 69.86) compared to male participants (Pre Md 130.08ms ± 76.45 to post Md 136.77ms ± 67.56), (p=0.025, ES 0.28). There were no significant differences between male and female participants in exercise-BDNF response and other cognitive measures.

4.5 Discussion

This study examined changes in sBDNF concentration and cognitive performance in response to a short bout of high intensity aerobic exercise in individuals with MCI. This is the first study to show that a short bout of high intensity aerobic exercise increases peripheral sBDNF in an MCI population. The results support previous work in this area which has primarily focused on young healthy cohorts (Ferris et al., 2007, Griffin et al., 2011, Vega et al., 2006, Winter et al., 2007, Tsai et al., 2014b, Tonoli et al., 2015, Tang et al., 2008, Hwang et al., 2016, Hötting et al., 2016). However, in the current study exercise induced increase in sBDNF did not lead to any significant between group differences in cognitive performance, with secondary analysis demonstrating only modest within group change.

The findings of the present study are consistent with previous studies that have reported increases in peripheral BDNF in response to acute exercise protocols in healthy adult cohorts (Ferris et al., 2007, Griffin et al., 2011, Vega et al., 2006, Winter et al., 2007, Tsai et al., 2014b, Tonoli et al., 2015, Tang et al., 2008, Hwang et al., 2016, Hötting et al., 2016) and in clinical populations (Gustafsson et al., 2009, Castellano and White, 2008). To date, few studies have examined the effect of acute aerobic exercise on peripheral BDNF in older adults (Coelho et al., 2014, Gomes et al., 2014, Babaei et al., 2014, Dimitrova et al., 2017, Håkansson et al., 2017) or MCI (Tsai et al., 2018). However, a recent study by Tsai et al. (2018) found an acute bout of 30 minutes of moderate intensity aerobic exercise significantly increased sBDNF levels in a group (n=25) of older adults with amnestic MCI. In agreement, findings indicate that older adults with MCI, despite being in the early stages of the neurodegenerative process, retain the ability to increase peripheral BDNF concentration following acute aerobic exercise of varying intensity and duration.

Across the literature, the percentage BDNF change in response to exercise varies widely in healthy and clinical populations, with an average increase of 60% reported in peripheral BDNF levels following acute exercise (Dinoff et al., 2017, Knaepen et al., 2010). The magnitude of BDNF change in response to exercise is dependent on blood lactate concentration, duration and intensity of exercise and is transient in nature (Schmidt-Kassow et al., 2014, Ferris et al., 2007, Tang et al., 2008, Saucedo Marquez et al., 2015, Schmolesky et al., 2013, Knaepen et al., 2010, Schiffer et al., 2011). The within group sBDNF change in response to exercise observed in our results was 7.07% (group A) and 15.7% (group B). Studies of similar study design that examined comparable graded exercise protocols in healthy young cohorts (Ferris et al., 2007, Griffin et al., 2011, Vega et al., 2006) and clinical populations (Laske et al., 2010, Coelho et al., 2014) reported higher % BDNF change in response to exercise (16%-30% relative change from baseline). Coelho et al. (2014) examined the exercise BDNF response in 21 older adults with AD and 18 healthy older adults and found significant increases in BDNF plasma levels in both groups ($p = 0.001$; $F = 13.63$; $df = 37$) with a relative change of 22% and 16% respectively. Despite comparable performance of the exercise condition (duration and intensity) in both groups, group B demonstrated a higher % increase in sBDNF post exercise. In contrast to existing literature, the BDNF upregulation did not appear to be driven by lactate (Schiffer et al., 2011), but may be explained by the significantly higher CR fitness observed in group B.

CR fitness in the present study cohort was low, with n=59 (92.2%) of participants categorised as very poor (<20 percentile) or poor (20-40 percentile) (ACSM, 2013). While evidence supports strong associations between higher levels of CR fitness and cognitive function (Wong et al., 2015, Smith et al., 2010), the relationship between BDNF and CR fitness is unclear, with some studies reporting a positive association between the two immediately after exercise (Cho et al., 2012) and others reporting an inverse relationship (Tomporowski, 2003, Jung et al., 2011, Currie et al., 2009). A meta-analytic review by Dinoff et al. (2017) reported significant associations between VO_2peak and effect sizes in studies measuring the effects of acute exercise on BDNF, indicating greater increases in peripheral BDNF after acute exercise in those with greater CR fitness. In the present study, we could not compare BDNF response in high and low fit participants due to the homogeneity in the study sample but no correlation was found between CR fitness (VO_2max) and baseline sBDNF levels.

Despite the consistently reported positive effects of acute exercise on cognitive performance (Piepmeier and Etnier, 2015, Winter et al., 2007, Skriver et al., 2014, Basso

et al., 2015, Hillman et al., 2003), the findings of the current study do not support the beneficial effect of acute exercise on cognitive performance in MCI. In contrast, the resting control condition demonstrated a decrease in sBDNF and improved performance on the SART, a task that activates the cortical and subcortical attentional networks (O'Connor et al., 2011). While it is possible that the resting control condition may have reduced circulating cortisol levels similar to quiet meditation practice (O'Leary et al., 2016, Fox et al., 2014), the mechanisms underpinning the observed effect cannot be fully explained with further research required.

Although a polarising topic in neuroscience research, sex differences in cognition have generally been disregarded as a confounder. A number of authors argue that biology is not a major determinant for sex differences in cognition and that these differences are overall small and negligible (Hyde and Linn, 2006, Hyde, 2005). In the current study, baseline measures of cognitive performance were comparable for male and female participants. Similarly, longitudinal studies of aging suggest no significant sex differences with regard to overall cognitive performance (Seeman et al., 2001). However, sex differences in SART RT were observed with females gaining significant improvement in RT following acute exercise compared to males. RTs are known to slow and become more variable with age, with significant sex differences reported in reaction time variability (Der and Deary, 2006). Despite recent reports of sex differences in the cognitive response in executive function tasks to exercise (Barha et al., 2017), we did not observe any sex differences in other cognitive measures in response to acute exercise.

Furthermore, findings did not reveal sex differences in BDNF at baseline or in response to acute exercise. Recent studies report that some functions or action mechanisms of BDNF may vary in a sex-dependent manner (Chan and Ye, 2017). The interaction between BDNF and sex steroids, namely oestrogen is thought to have a positive regulatory effect on BDNF expression and signalling. Therefore, hormonal status can greatly influence the expression of BDNF and the disruption of the relationship between oestrogen and BDNF (such as in the case of menopause) is thought to contribute to neurological disorders associated with the hippocampus, such as AD (Scharfman and MacLusky, 2005, Sohrabji and Lewis, 2006). A meta-analytic review and RCT report that the BDNF response to acute and chronic exercise may vary in a sex-dependent manner (Dinoff et al., 2017, Baker et al., 2010c) with significant increases observed in males but not in females. In contrast, our findings did not reveal sex differences in the BDNF response to acute exercise.

4.6 Conclusion

The results of this study indicate that a single session of high intensity exercise is feasible in an MCI cohort, enhances circulating sBDNF concentration but does not improve visuospatial learning and memory, sustained attention or executive function. This research adds to the literature which postulates that the impaired BDNF profile in MCI cohorts may be amenable to exercise training as a strategy to address the declining BDNF profile.

5 Chapter 5: Study II: A comparison of contrasting aerobic exercise protocols on serum brain derived neurotrophic factor concentration and cognitive performance in mild cognitive impairment

5.1 Introduction

Given the generally reported facilitative effect of acute exercise on cognitive performance, it is important for research to explore dose–response characteristics in clinical populations to help define the optimal level of acute exercise for cognitive benefit (Chang et al., 2012, Lambourne and Tomporowski, 2010). Acute effects of exercise help provide an understanding of the underlying mechanisms by which the brain adapts to habitual exercise (Weng et al., 2017).

Within the literature, a number of moderators of the acute exercise and cognitive relationship have been identified including exercise intensity and duration (Chang et al., 2012, Lambourne and Tomporowski, 2010). Specific to duration, research suggests that exercise ranging from 11 minutes (Chang et al., 2012) to 40 minutes (Tomporowski 2010) are effective in eliciting exercise induced cognitive change (Lambourne and Tomporowski, 2010, Roig et al., 2013). However, a curvilinear dose-response between exercise duration and cognitive performance has been suggested, with 20 minutes of exercise reported as the optimum duration in a group of young males, with shorter or longer durations demonstrating negligible benefits (Chang et al., 2015).

Exercise intensity, a more complex concept, has garnered a great deal of attention within this field of research. Several studies (Chmura et al., 1994, Arent and Landers, 2003, Perini et al., 2016), narrative reviews (Best, 2010, McMorris and Graydon, 2000, Tomporowski, 2003, Brisswalter et al., 2002) and meta-analyses (Chang et al., 2012, Lambourne and Tomporowski, 2010, Etnier et al., 1997) have suggested an inverted U-shaped relationship between acute exercise and cognition, with moderate intensity exercise considered most effective in increasing physiological arousal and the amount of allocatable resources, thereby facilitating cognition (Yerkes and Dodson, 1908). In contrast, the ‘drive theory’ is also supported within the literature, with studies demonstrating a linear dose–response trend during exercise, such that increased exercise intensity is directly related to improved cognitive performance with the largest

effects observed at high intensity (Chang et al., 2009, Davranche and Audiffren, 2004, Landers, 1980).

With exercise intensity considered important in determining magnitude of change in physiological mechanisms (heart rate, catecholamines and magnitude of BDNF increase), an intensity driven change across these physiological mechanisms may be important for predicting the cognitive effect following acute exercise. A review of acute exercise by Knaepen et al. (2010) described the positive relationship between exercise intensity and BDNF concentrations, indicating that high intensity protocols result in larger increases in BDNF concentration over low-intensity protocols. Thus, if BDNF is a mediator of the effects of acute exercise on cognitive performance, intensity would be expected to influence behavioural (cognitive) outcomes.

While initial results are promising that both maximal and submaximal intensities show positive effects on cognitive performance, further research is necessary to clarify the dose-response effect. The contradictory findings in experimental research has led to the identification of several methodological factors to control in studies including the intensity and duration of exercise (Brisswalter et al., 2002). This study was designed to investigate contrasting aerobic exercise protocols and examine whether a short bout high intensity aerobic exercise or a longer duration (45 minutes) of moderate intensity aerobic exercise has a greater impact on serum BDNF (sBDNF) concentration and cognitive performance in a Mild Cognitive Impairment (MCI) cohort.

5.2 Aims and objectives

The aim of this study was to compare the effect of two distinct aerobic exercise protocols on sBDNF concentration and cognitive performance in an MCI cohort. The specific objectives were:

- To evaluate the sBDNF response to a short bout of high intensity exercise compared to a longer bout of moderate intensity exercise
- To compare the effect a short bout of high intensity exercise and a long bout of moderate intensity exercise on a selection of cognitive tasks measuring visuospatial learning and memory, sustained attention and executive function

5.3 Methods

5.3.1 Participant recruitment

Participant recruitment, diagnostic, inclusion and exclusion criteria to all studies presented in this thesis is described in Chapter 2, Section 2.3.2 – 2.3.5. Only participants randomised to the aerobic intervention arm of the NeuroExercise study participated in the study presented in this chapter.

5.3.2 Study design

Using a within-subject study design, each participant acted as their own control and completed two experimental exercise conditions. Firstly, participants completed exercise condition A - a short bout of high intensity aerobic exercise. One week later, participants completed exercise condition B - a longer (45 minute) bout of moderate intensity aerobic exercise (Figure 5:1). Blood sampling and cognitive testing was performed at rest (pre exercise) and immediately post the aerobic exercise condition. The difference pre-post exercise was calculated and compared between the two experimental exercise conditions.

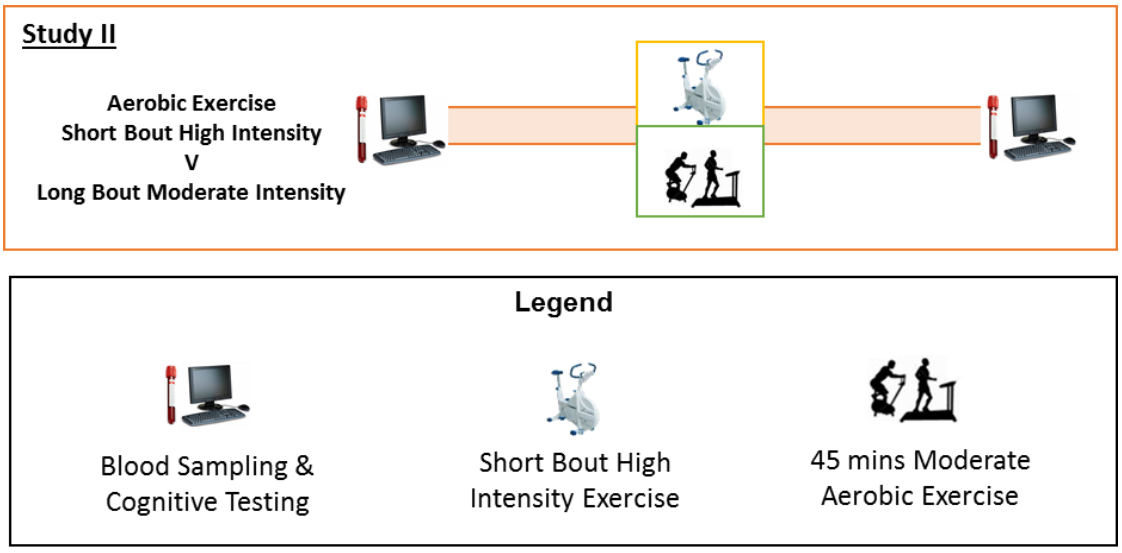

Figure 5:1 Outline of study design, intervention and outcome assessments in Study II

5.3.3 Outcomes

5.3.4 Blood sampling

Blood samples were collected in a resting state (pre exercise) and within 0-10 minutes post each exercise condition. The procedure is outlined in Chapter 2, Section 2.5.1 – 2.5.3.

5.3.5 Cognitive performance

Following blood sampling, cognitive measures were administered pre and post both exercise conditions. These included:

1. CANTAB Paired Associate Learning (PAL) task, a measure of visuospatial learning and memory.
2. Sustained Attention to Response Task (SART), a computerised Go-No-Go paradigm measuring sustained attention
3. Stroop Neuropsychological Screening Test (Stroop) measuring executive function

Testing took approximately 30 minutes to complete. Full details on the psychometric properties and the standardised administration of each cognitive test is outlined in Chapter 2, Section 2.5.2 – 2.5.8.

5.4 Intervention

There was a washout period of at least one week between the experimental exercise conditions. Details of both exercise conditions can be found in Chapter 2 Methodology.

5.4.1 Condition A: Short duration high intensity

Condition A involved a short bout of high intensity aerobic exercise. High (maximal) intensity exercise is typically defined as exercise above 85% of VO_2max during which energy supply is derived from anaerobic energy systems (Norton et al., 2010). See Section 2.4.1 for full details.

5.4.2 Condition B: Long duration moderate intensity

Condition B consisted of a longer bout (45 minutes) of moderate intensity aerobic exercise. Moderate intensity exercise is typically defined as exercise at submaximal workloads during which energy supply is derived from aerobic energy systems (Norton et al., 2010). See section 2.4.2 for full details.

5.4.3 Statistical analysis

SPSS 24 (SPSS Inc; Chicago, IL, USA) was used for analysis with statistical significance set at $p<0.05$. All data are presented as mean ± SD for normally distributed data and median ± IQR for non-normally distributed data. Preliminary analyses were performed to ensure no violation of the assumptions of normality by visual inspection of histogram and Q-Q plots and using Kolmogorov-Smirnov test ($p>.05$). As the same participants acted as their own control (completing condition A and condition B), the following statistical approach was used. The difference in BDNF and measures of cognitive performance was calculated pre to post exercise condition A and exercise condition B. To compare the difference between the two conditions, paired samples t-tests were performed on normally distributed data and Wilcoxin signed rank test was used for non-normally distributed data.

5.5 Results

Participants were enrolled from February 25th, 2016 and data collection for this study ended on Sept 25th, 2017. A total of 19 participants completed exercise condition A and 18 participants completed exercise condition B. One participant dropped out of the study after completing exercise condition A. Missing data includes missed venepuncture (condition A pre exercise) n=1, missing PAL due to refusal to complete (condition A) n=1, missing SART due to incomplete / missing data n=1 and invalid Stroop due to colour-blindness n=1 (both time points).

5.5.1 Exercise parameters

Table 5-1 Exercise prescription parameters collected during condition A (short bout high intensity) and condition B (long bout moderate intensity). Time for condition B was a standardised time of 45 minutes of exercise at the prescribed intensity.

Exercise parameters	Condition A n=19	Condition B n=18
Time (minutes:seconds)	10:13 (2:11)	45:00
Max HR (HR_{max})	115 (31)	110 (17)
Rate of Perceived Exertion (RPE)	-	13.4 (1.0)
Max watts ($Watts_{max}$)	107 (31)	-
Peak lactate (mmol/L)	4.1 (1.5)	-
Lactate change (mmol/L)	2.0 (1.8)	-
Respiratory Exchange Ratio (RER)	1.03 (0.10)	-

Exercise condition A was performed for 10 minutes 13 seconds (± 2 minutes 11 seconds) with a HR_{max} of 115 (± 31) and a peak lactate of 4.1 mmol/L (± 1.5). The duration of exercise included a 3-minute period of cycling unloaded. Respiratory Exchange Ratio (CO_2 production/O_2 uptake) determined through subjects' breath by breath samples was 1.03 (± 0.10). Exercise condition B was performed for a standardised time of 45 minutes continuous exercise. The mean HR_{max} was 110 (± 17) and the mean RPE was 13.4 (± 1.0) across classes (Table 5-1).

5.5.2 Participant characteristics

Participant demographic and clinical characteristics include the following: age, sex, education, Montreal Cognitive Assessment (MoCA) and Body Mass Index (BMI) and cardiorespiratory fitness level (VO_2max) (Table 5-2). Participants (n=19) had a mean age of 72.7 years (± 5.7), marginally more males to females (10 males, 52.63%); and all were Caucasian (100%). Participants had high levels of education (13.4 ± 3.7 years) and all participants had MoCA scores within the inclusion criteria range of 18-26 with a mean score of 21.6 (± 2.6). Participants had a mean BMI of 27.48 kg/m^2 (± 4.79) indicating a tendency towards being overweight and had low levels of cardiorespiratory (CR) fitness (VO_2max) with a mean VO_2max of 19.63ml/kg/min (± 3.57). Based on age and gender population norms, 84.2% (n=16) were classed as having very poor CR fitness (< 20^{th}

percentile) and the remaining 15.8% (n=3) classed as poor CR fitness (20^{th}-40^{th} percentile).

Table 5-2 Baseline participant characteristics Study II. Data are presented as mean ± SD for normally distributed data and as median ± IQR for non-normally distributed data.

	Aerobic Group
Variable	**n=19**
Gender (M/F)	10 / 9
Age (years)	72.7 (5.7)
Education (years)	13.4 (3.7)
MoCA	21.6 (2.6)
BMI (kg/m^2)	27.48 (4.79)
VO_2max (mL/kg/min)	19.63 (3.57)

5.5.3 Difference between conditions: BDNF

sBDNF concentration decreased from 8943.14 $pg \cdot ml^{-1}$ (± 6072.12) to 7735.41 $pg \cdot ml^{-1}$ (± 4715.08) immediately post high intensity exercise (condition A) and increased from 1397.53 $pg \cdot ml^{-1}$ (± 624.07) to 1506.55 $pg \cdot ml^{-1}$ (± 388.49) following 45 minutes moderate intensity exercise (condition B), however the difference between the groups was not significant ($z = -1.035$, $p = 0.30$) (Table 5-3). The overall relative change in sBDNF concentration was small with a change of -4.58% (± 24.44%) in response to condition A and 4.99% (± 48.40%) in response to condition B.

5.5.4 Difference between conditions: cognitive performance

The change in cognitive test scores between T1 to T2 was calculated and compared between the two conditions. Error rate on the PAL task increased slightly in condition A from 41.89 (± 17.90) to 44.06 (± 18.35) and also in condition B from 38.06 (± 17.44) to 39.78 (± 18.64), with no difference between the exercise conditions ($t(16) = .533$, $p = 0.60$). The number of correct responses on the Stroop CWS increased from 67.33 (± 29.62) to 70.28 (± 34.37) in condition A and decreased from 73.82 (± 29.02) to 67.82 (± 36.84) in condition B, with no significant difference between the two conditions ($z = -1.446$, $p = 0.14$). SART commission errors remained largely unchanged following both exercise conditions (condition A from 2.00 ± 3.00 to 4.00 ± 3.00; condition B from 2.50 ± 4.00 to 2.50 ± 3.00), with no difference between conditions ($t(16) = -.869$, $p = 0.39$). Finally, reaction time demonstrated a large degree of variability but decreased in

condition A from 146.39ms (± 62.95) to 124.80ms (± 105.30) and increased from 103.93ms (± 130.07) to 113.26ms (± 97.75) in condition B, with no difference between the conditions (t (14) = -.627, p = 0.54). See Table 5-3 for absolute values.

Table 5-3 Effects of contrasting aerobic exercise protocols on BDNF and cognitive outcomes. Data are presented for group A: short bout high intensity aerobic exercise and group B: longer bout moderate intensity aerobic exercise. Data is documented as mean ± SD for normally distributed data and as median ± IQR for non-normally distributed data. The p-value represents the difference between each condition as calculated by pre-post exercise. BDNF: Brain Derived Neurotrophic Factor. PALTEA: Paired Associate Learning Total Errors Adjusted. CWS: Colour Word Score. SART: Sustained Attention to Response Task. CE: Commission Errors. RT: Reaction Time.

Variable		T1: Pre-exercise	T2: Post Exercise	Difference pre-post exercise	p-value
BDNF (pg·ml^{-1})					
	Condition A	8943.14 (6072.12)	8357.62 (5324.72)	-585.51 (3017.42)	0.39
	Condition B	1397.53 (624.07)	1565.55 (452.45)	168.02 (667.57)	
BDNF outliers removed (pg·ml^{-1})					
	Condition A	8943.14 (6072.12)	7735.41 (4715.08)	-218.64 (4050.35)	0.30
	Condition B	1397.53 (624.07)	1506.55 (388.49)	165.74 (688.04)	
PALTEA					
	Condition A	41.89 (17.90)	44.06 (18.35)	2.17 (12.12)	0.60
	Condition B	38.06 (17.44)	39.78 (18.64)	1.72 (15.42)	
Stroop CWS					
	Condition A	67.33 (29.62)	70.28 (34.37)	1.50 (16.00)	0.14
	Condition B	73.82 (29.02)	67.82 (36.84)	-6.00 (18.82)	
SART CE					
	Condition A	2.00 (3.00)	4.00 (3.00)	0.78 (2.81)	0.39

	Condition B	2.50 (4.00)	2.50 (3.00)	0.06 (2.01)	
SART RT (ms)					
	Condition A	146.39 (62.95)	124.80 (105.30)	-11.65 (46.24)	0.54
	Condition B	103.93 (130.07)	113.26 (97.75)	5.40 (59.94)	

5.6 Discussion

The present study compared the effect of a short bout of high intensity aerobic exercise and a long bout moderate intensity exercise on a selection of cognitive tasks and evaluated the BDNF response in these contrasting aerobic exercise conditions. In a small group of older adults with MCI, no significant difference in sBDNF concentration or measures of cognitive performance (visuospatial learning and memory, sustained attention and executive function) between these two contrasting acute aerobic exercise conditions was observed. Results are equivocal but do not lend support to the hypothesis that post exercise BDNF response or cognitive performance is variably affected by exercise intensity.

There was no difference in BDNF response regardless of whether exercise was performed for a short duration at high intensity or a longer duration at moderate intensity. Surprisingly, results showed that in the same group of participants, a short bout of high intensity aerobic exercise led to a slight decrease in sBDNF concentration (-4.45% ± 24.44%) while a long bout moderate intensity exercise marginally increased sBDNF concentration (4.99% ± 48.40%). Sustained periods of moderate intensity exercise have demonstrated upregulation of BDNF, particularly in healthy young cohorts (Zoladz et al., 2008, Tsai et al., 2014a). However, the BDNF response following condition A is in contrast with the existing literature that supports the upregulation of peripheral BDNF following high intensity acute aerobic exercise interventions (Vega et al., 2006, Heyman et al., 2012, Coelho et al., 2014). These results should be interpreted with caution as this study was potentially underpowered.

In the current study, cognitive performance did not differ significantly between a short bout of high intensity aerobic exercise and a longer bout of moderate intensity exercise. To date, only a small number of experimental studies have examined moderate and high intensity acute exercise paradigms in MCI cohorts and these results have demonstrated only modest improvements in selective cognitive tasks. Segal et al. (2012) found 6 minutes at 70% VO_2max (high intensity) on a stationary bicycle significantly elevated endogenous norepinephrine and retrogradely enhanced memory performance in a group with amnestic MCI (n=23). In another group with amnestic MCI, Tsai et al. (2018) demonstrated the upregulation of peripheral BDNF following 30 minutes moderate intensity (65-75% Heart Rate Reserve) aerobic exercise (n=25). However, despite the BDNF increase, accuracy rate on the Flanker task (executive function) did not change, but reaction times did reduce significantly in the aerobic group compared to the control

group (Tsai et al., 2018). Within the literature, it has been suggested that high intensity exercise using anaerobic metabolism and hypocapnia, can result in constriction of cerebral vessels and may adversely affect cognitive performance (Severinghaus and Lassen, 1967, Wasserman and Patterson, 1961). While high intensity exercise induces greater physiological and psychological stress, the increased cortisol and catecholamine release may be beyond the optimal point for cognitive performance, may cause physical and psychological fatigue thereby reducing attention resources available for the cognitive task (McMorris and Keen, 1994, Covassin et al., 2007, Tomporowski, 2003, Lambourne and Tomporowski, 2010, McMorris, 2016).

Participants in the current study had fitness levels of 19.63 mL/kg/min (± 3.57), which is categorised as poor or very poor in comparison to population norms. Cardiorespiratory (CR) fitness is a known important moderator variable, an essential component of physical fitness and is closely related to enhanced cognitive functioning across the lifespan (Hillman et al., 2008, McAuley et al., 2013). Throughout the literature, high-fit individuals generally show greater levels of cognitive functioning compared to their low-fit counterparts, especially in prefrontal cortex-dependent tasks (Guiney and Machado, 2013). Research has demonstrated greater cognitive benefits from acute exercise in individuals with high fitness (Chang et al., 2012, Budde et al., 2012) or highly trained older participants relative to those with low-to-moderate levels of fitness or those who are untrained (Pesce and Audiffren, 2011, Pesce et al., 2011). However, due to small sample size in our study and homogeneity (low cardiorespiratory fitness) of the group, we were unable to compare high fit and low fit groups. It is also plausible, given the low CR fitness of participants that both exercise conditions may have had a fatiguing effect and impaired post exercise cognitive performance.

The cognitive outcomes in the present study measured visual learning and memory (hippocampal dependant memory task), sustained attention and executive function (both components of executive control), which are all considered complex higher level cognitive processes. Results indicate that selective components of higher level cognitive processes do not demonstrate immediate post exercise change in an MCI cohort. Research suggests that specific cognitive domains are amenable to acute exercise change and studies of acute exercise in healthy younger cohorts have predominantly measured prefrontal cortex-dependent functions, such as information processing, reaction time, attention, crystalized intelligence, executive functioning, and memory (Chang et al., 2012, Loprinzi and Kane, 2015), although not all prefrontal cortex-dependent tasks have consistently shown improvements by acute exercise (Nanda et

al., 2013). Across experimental studies, cognitive performance at rest versus cognitive performance after high intensity or moderate intensity has produced inconsistent results and studies have reported both the positive and negative effects of acute exercise on cognitive performance results (Griffin et al., 2011, Ferris et al., 2007, Winter et al., 2007, Labban and Etnier, 2011, Coles and Tomporowski, 2008, Hwang et al., 2016, Kao et al., 2017) while others report negligible or no effects (Lambourne, 2012, McMorris and Hale, 2012). Results in a number of these studies have been limited to lower-level cognitive performance tasks, and hence, may not apply to higher-order processes such as executive control or memory tasks. Dietrich and Audiffren (2011) suggest that exercise may lead to decreases in cognitive function during more cognitively demanding tasks. It has been further suggested that lower level cognitive tasks can produce measurable cognitive change in response to acute exercise and that high-level cognitive tasks particularly hippocampal-dependent cognition, may require structural adaptive brain changes that are accrued from chronic exercise (Basso and Suzuki, 2017, Basso et al., 2015).

5.7 Conclusion

This study did not establish measurable differences in cognitive performance or BDNF concentration when two contrasting acute aerobic exercise conditions (short bout high intensity vs long bout moderate intensity) were compared. Based on the paucity of evidence supporting the role of acute exercise in enhancing cognitive performance in MCI cohorts, limited conclusions can be drawn and further research addressing the methodological limitations of the current study is warranted.

6 Chapter 6: Study III: An investigation of two distinct acute exercise paradigms on serum brain derived neurotrophic factor concentration and cognitive performance in mild cognitive impairment

6.1 Introduction

Acute exercise paradigms vary in the modality, intensity and duration of exercise, with the majority of existing research surrounding the acute exercise-cognitive relationship investigating changes in cognitive performance after an acute bout of aerobic exercise. Similarly, the vast majority of studies examining the effect of acute exercise on blood concentrations of BDNF have focused on aerobic activity (Dinoff et al., 2017). Within the literature, there is a paucity of acute exercise studies in MCI cohorts and this study was designed to add to the small body of existing research in this population, to help establish the relevance of acute exercise.

The exercise paradigms in the current study represented two distinct exercise modalities characterised by different physiological demands and response (cardiovascular, musculoskeletal, metabolic). Given the limited research on exercise modes, this study examined the effect of a single bout of 45-minutes of moderate intensity aerobic exercise (AT) compared to 45-minutes balance and toning (BAT) exercise on serum BDNF (sBDNF) concentration and cognitive performance in a group of largely sedentary, low fit individuals with MCI. The testing was performed during week one of a one year structured exercise intervention, thereby minimising any potential training effects. Based on the existing research that supports acute moderate intensity aerobic exercise, it was predicted that a greater upregulation of BDNF and improved cognitive performance would be observed in the AT group compared to the BAT (active control) group.

6.2 Aims and objectives

The aim of the current study was to investigate the effect of two distinct acute exercise modalities on sBDNF concentration and cognitive performance (visuospatial learning and memory, sustained attention and executive function) in individuals with MCI. The change in sBDNF concentration and cognitive performance pre-post a single session of exercise was compared between both groups (moderate intensity AT versus non-aerobic BAT). The specific objectives were:

- To examine change in sBDNF concentration in an MCI cohort and to compare the change in sBDNF concentration pre-post acute exercise between two distinct exercise conditions
- To explore pre-post acute exercise change in cognitive performance (visuospatial learning and memory, sustained attention and executive function) in an MCI cohort and to compare the change in cognitive performance between two distinct exercise conditions

6.3 Methods

6.3.1 Participant recruitment

Participant recruitment, diagnostic, inclusion and exclusion criteria to all studies presented in this thesis is described in Chapter 2, Section 2.3.2 – 2.3.5. The participants in the current study represent those randomised to the structured one year AT intervention or equivalent BAT (non-aerobic) intervention groups of the NeuroExercise study.

6.3.2 Study design

Participants were randomised to either a 48-week AT intervention (n=19) or BAT (non-aerobic) (n=22) equivalent following baseline assessment. This experimental study had a pre-post-test design with measurements taking place during week one of a one year structured exercise intervention to minimise the potential of any training effects accrued over time. Resting blood sampling and cognitive testing were completed (outlined in detail in Chapter 2, Section 2.5), followed an immediate post exercise repeated measure of blood sampling (0-10 minutes of completed exercise) and cognitive testing (See Figure 6:1).

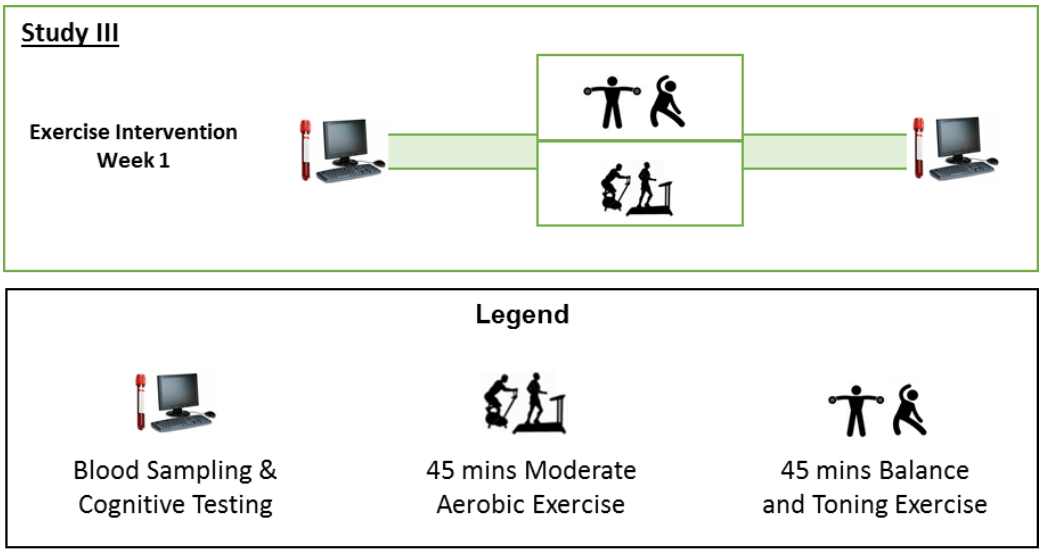

Figure 6:1 Study design showing study outcome measures and intervention in Study III

6.3.3 Outcomes

6.3.4 Blood sampling

Blood samples were collected pre exercise and within 0-10 minutes post each exercise condition. The procedure is outlined in Chapter 2, Section 2.5.1 – 2.5.3.

6.3.5 Cognitive performance

Following blood sampling, cognitive measures were administered pre and post both exercise conditions. These included:

1. CANTAB Paired Associate Learning (PAL) task, a measure of visuospatial learning and memory.
2. Sustained Attention to Response Task (SART), a computerised Go-No-Go paradigm measuring sustained attention
3. Stroop Neuropsychological Screening Test (Stroop) measuring executive function

Testing took approximately 30 minutes to complete. Full details on the psychometric properties and the standardised administration of each cognitive test is outlined in Chapter 2, Section 2.5.5 – 2.5.8.

6.3.6 Exercise conditions

A standardised 45-minute duration of exercise was applied in both conditions, with intensity and modality of exercise manipulated. The AT condition consisted of a 45-

minute bout of moderate intensity exercise. The BAT condition completed 45 minutes of largely non-aerobic activities. Both exercise conditions are outlined in detail in Chapter 2, Section 2.4.2 and 2.4.3.

6.3.7 Statistical analysis

SPSS 24 (SPSS Inc; Chicago, IL, USA) was used for analysis with statistical significance set at $p<0.05$. All data are presented as mean ± SD for normally distributed data and median ± IQR for non-normally distributed data. Preliminary analyses were performed to ensure no violation of the assumptions of normality using Kolmogorov-Smirnov test ($p>.05$). Visual inspection of Q-Q plot (to look for systematic deviations) and histogram was performed (to examine skew). Baseline values for all variables were compared between the two groups using an Independent samples t-test for normally distributed data and using a Mann-Whitney U Test for non-normally distributed data. The difference in BDNF and cognitive performance scores from pre to post exercise was calculated in both exercise groups. Between group differences were analysed using an Independent samples t-test for normally distributed data and using a Mann-Whitney U Test for non-normally distributed data. Pearson product-moment correlation coefficient (r) and Spearman Rank Order Correlation (rho) were used as appropriate to identify correlations between study variables with BDNF concentrations.

6.4 Results

Two participants dropped out of the NeuroExercise study after baseline assessment and randomisation, n=1 from the AT group and n=1 from the BAT group. Missing data includes n=4 Stroop tests (n=2 invalid for colour-blindness, n=1 from AT and n=1 BAT with a further n=2 participants refusing to complete the Stroop task from BAT group). All other measures collected were complete.

6.4.1 Participant characteristics

Participant demographic and clinical characteristics collected prior to completing exercise condition A included the following: age, sex, education, Montreal Cognitive Assessment (MoCA) and Body Mass Index (BMI) and fitness level (VO_2max) (Table 6-1). Participants (n=41) had a mean age of 71.4 years (± 5.9), marginally more males (23 males, 56.1%); and all were Caucasian (100%). Participants has a tendency towards higher levels of education (13.32 ± 3.65 years) and all participants had MoCA scores within the inclusion criteria range of 18-26, with a mean score of 21.98 (± 2.52).

Participants had a mean BMI of 27.49 kg/m^2 (± 4.70) and low levels of cardiorespiratory fitness (VO_2max 19.63 ± 5.56 mL/kg/min). There were no significant between group differences in baseline characteristics.

Table 6-1 Baseline participant characteristics Study III. Data are presented as mean ± SD for normally distributed data and as median ± IQR for non-normally distributed data. Note statistical significance; *p < .05

Variable	AT n=19	BAT n=22	p-value
Gender (M/F)	10/9	13/9	0.32
Age (years)	72.42 (5.74)	70.55 (6.18)	0.68
Education (years)	13.42 (3.74)	13.23 (3.66)	0.86
MoCA	21.63 (2.67)	22.27 (2.41)	0.42
BMI (kg/m^2)	27.48 (4.79)	27.49 (4.74)	0.99
VO_2max (mL/kg/min)	19.63 (3.57)	19.62 (6.92)	0.99

Baseline BDNF concentrations and all measures of cognitive performance were comparable between groups (Table 6-2).

Table 6-2 Baseline study variables Study III. Data are presented as mean ± SD for normally distributed data and as median ± IQR for non-normally distributed data. Note statistical significance; *p < .05. BDNF: Brain Derived Neurotrophic Factor. PALTEA: Paired Associate Learning Total Errors Adjusted. CWS: Colour Word Score. SART: Sustained Attention to Response Task. CE: Commission Errors. RT: Reaction Time.

Variable	AT n=19	BAT n=22	p-value
BDNF (pg·ml^{-1})	1397.53 (624.07)	1323.75 (539.14)	0.69
BDNF outliers excl.	1340.81 (593.53)	1261.51 (469.40)	0.65
PALTEA	38.06 (17.44)	36.52 (17.72)	0.74
Stroop CWS	73.82 (29.02)	75.60 (31.14)	0.85
SART CE	2.5 (4)	2 (3)	0.74
SART RT (ms)	103.93 (130.07)	137.05 (66.89)	0.28

6.4.2 Brain Derived Neurotrophic Factor

sBDNF concentration increased by 165.74 pg·ml^{-1} (± 688.04) in the AT group and decreased by -115.64 pg·ml^{-1} (± 350.73) in the BAT (control) group. This represented a 50.3% (± 119.72%) increase from baseline in the AT group and a -3.8% (± 31.13%) decrease in the BAT group. However, changes in BDNF concentration pre-post exercise was not significantly different between groups, t (23) = 1.51, p = .14 (Table 6-3).

At baseline, BDNF did not correlate with visuospatial learning and memory (rho = .23, p = .16), executive function (r = -.183, p = .29) or sustained attention (rho = -.15, p = .37). Baseline serum BNDF concentration was similar for male (M = 1280.59 ± 470.77) and female (M = 1326.45 ± 619.33) participants (p = .80) and change pre-post exercise in the AT group did not differ significantly between males (mean change 303.91 pg·ml^{-1} ± 734..47) and females (mean change -31.65 pg·ml^{-1} ± 613.16), t (15) = .98, p = .33.

6.4.3 Cognitive performance

The number of errors (PALTEA) on the visuospatial learning and memory task increased in the AT group (mean change= 1.72 ± 15.42) and decreased in the BAT group (mean change = -4.19 ± 11.27), with no significant difference between the groups (t (37) = -1.38, p = .17, mean difference = -5.91, 95% CI: -14.59 – 2.77). Following exercise, the AT group made fewer correct responses on the Stroop CWS (mean change = -6.00 ± 18.82), while the BAT group made a higher number of correct responses (mean change = 4.39 ± 17.49). Again, the changes on this executive function task did not differ significantly between groups (t (33) = -1.69, p = .10, mean difference = -10.38, 95% CI: -22.87 – 2.09). There was no observable change in commission error rate on the sustained attention task (AT: mean change = 0.06 ± 2.01, BAT: mean change = 0.33 ± 2.35, t (37) = -.39, p = .69, mean difference = -.27, 95% CI: -1.71– 1.15), with no significant difference between groups (t (37) = -.39, p = .69, mean difference = -.27, 95% CI: -1.71– 1.15). Finally, reaction time on the sustained attention task increased in both the AT (AT: median change = 0.53 ms ± 44.48 ms) and BAT group (median change = 4.12 ms ± 32.60ms) following exercise, with no difference between the groups (U = 182.00, z = .06, p = .96, r=0.009). See Table 6-3 for absolute values.

Table 6-3 Between group differences in study variable at T1 and T2 time points. Data are presented for the AT and BAT group as mean ± SD for normally distributed data and as median ± IQR for non-normally distributed data. Note p-value represents within group differences with statistical significance; *p < .05. BDNF: AT: Aerobic training. SAT: Stretching and toning. BDNF: Brain Derived Neurotrophic Factor. PALTEA: Paired Associate Learning Total Errors Adjusted. CWS: Colour Word Score. SART: Sustained Attention to Response Task. CE: Commission Errors. RT: Reaction Time

Variable		T1: Pre-exercise	T2: Post Exercise	Within Group Change	Between Group Analysis p-value
BDNF (pg·ml^{-1})					
	AT	1397.53 (624.07)	1565.55 (452.45)	168.02 (667.57)	0.06
	BAT	1323.75 (539.14)	1108.79 (457.81)	-209.75 (541.91)	
BDNF outliers removed					
(pg·ml^{-1})	AT	1340.81 (593.53)	1506.55 (388.49)	165.74 (688.04)	0.14
	BAT	1261.51 (469.40)	1137.11 (451.33)	-115.64 (350.73)	
PALTEA					
	AT	38.06 (17.44)	39.78 (18.46)	1.72 (15.42)	0.17
	BAT	36.52 (17.72)	32.33 (16.96)	-4.19 (11.27)	
Stroop CWS					
	AT	73.82 (29.02)	67.82 (36.84)	-6.00 (18.82)	0.10
	BAT	75.60 (31.14)	83.06 (21.77)	4.39 (17.49)	
SART CE					
	AT	2.5 (4)	2.5 (3)	0.06 (2.01)	0.69
	BAT	2 (3)	3 (3)	0.33 (2.35)	

SART RT (ms)					
	AT	103.93 (130.07)	113.26 (97.75)	0.53 (44.48)	0.96
	BAT	134.83 (66.89)	114.10 (69.95)	4.12 (32.60)	

6.5 Discussion

The present study compared the effect of two distinct acute exercise modalities of equivalent duration on sBDNF concentration and cognitive performance in older adults with MCI. This study examined an aerobic exercise dose (45 minutes moderate intensity) commonly recommended within national and international physical activity guidelines (Health and Children, 2009, World Health Organization, 2010), which has applicability to the wider population. Furthermore, BDNF was investigated as a potential mechanism underlying the association between acute aerobic exercise and cognitive performance. The results revealed no significant difference pre-post exercise in sBDNF concentration or measures of visuospatial learning and memory, sustained attention or executive function in the AT group compared to the BAT group.

While not significantly different between groups, results demonstrated an exercise induced increase in sBDNF concentration in the AT group (50.3% ± 119.72% change relative from baseline) and a minor decrease in the BAT group (-3.8% ± 31.13% change relative from baseline). Studies have reported significant increases in peripheral BDNF following acute moderate intensity exercise across a range of neurological and psychiatric disorders including stroke (Morais et al., 2018), depression (Laske et al., 2010), Parkinson's disease (Zoladz et al., 2014) and multiple sclerosis (Gold et al., 2003), suggesting that this trophic factor has capacity to increase following exercise despite the presence of neurodegenerative or psychiatric disease. Existing literature broadly supports changes in BDNF as a function of both moderate and high intensity acute exercise in healthy populations (Ferris et al., 2007, Griffin et al., 2011, Skriver et al., 2014, Tonoli et al., 2015, Winter et al., 2007, Tsai et al., 2014a). In a group of healthy adult males, Schmolesky et al. (2013) et al found a 32% increase in peripheral BDNF relative to baseline across four exercise groups (moderate or high intensity exercise for 20 or 40 minutes). In this study, 40 minutes of moderate intensity cycling resulted in a 30.16% (± 76.11%) increase in BDNF concentration. Similar results were reported by Etnier et al. (2016) who found that BDNF did not change in the expected dose-response relative to exercise intensity. Results indicated that three conditions of varying intensity resulted in similar relative change in BDNF concentration following acute exercise (VO_2max: 43% increase; ventilatory threshold +20%: 48% increase; ventilatory threshold -20%: 37% increase). While the upregulation of BDNF following moderate and high intensity exercise is well supported in the literature (Saucedo Marquez et al., 2015, Morais et al., 2018), limited evidence supports low intensity exercise as an effective

strategy to augment BDNF (McDonnell et al., 2017, Jeon and Ha, 2017). In agreement with this, BDNF concentration was largely unchanged in response to acute BAT exercise in the current study.

Interestingly, similar to previous studies in this thesis, acute exercise did not demonstrate measurable change in cognitive performance. Despite the increase in BDNF within the AT group, performance appeared to decline on a visuospatial learning and memory and executive function task. In contrast, despite a slight decrease in BDNF in the BAT group, marginal improvements on the visuospatial learning and memory and executive function task were noted. This observation leads to questions regarding the reliability and validity of BDNF as a marker of cognition. At baseline, sBDNF concentration did not correlate with visuospatial learning and memory, executive function or sustained attention. Within existing literature, little is known about the association of peripheral BDNF levels with cognition. Some authors have suggested peripheral BDNF as a novel marker for impaired memory and general cognitive function across general and clinical populations (Komulainen et al., 2008, Levada et al., 2016, Vinogradov et al., 2009), while other have questioned the reliability of this as a potential cognitive biomarker (Driscoll et al., 2012, Penadés et al., 2018, Luan et al., 2017). However, it must be noted that this study was underpowered and considered exploratory in nature. Questions remain regarding the interaction between acute and chronic exercise paradigms relative to BDNF and cognitive performance. These questions will be answered in subsequent chapters within this thesis (Study IV and V, Chapter 7 and 8).

6.6 Conclusion

In conclusion, moderate intensity aerobic exercise upregulates BDNF, but the change pre to post exercise did not differ significantly in an aerobic exercise group compared to a non-aerobic exercise group. Acute aerobic exercise performed for 45 minutes did not lead to any measurable cognitive change in an MCI cohort.

7 Chapter 7: Study IV: The impact of acute and chronic exercise on serum brain derived neurotrophic factor concentration and cognitive performance following 6 and 12 weeks of structured exercise training in mild cognitive impairment

7.1 Introduction

The large number of studies assessing the impact of exercise on peripheral BDNF circulation indicates the importance of this topic. Reviews on the effect of exercise on basal BDNF concentrations in human subjects have generally reported a transient increase in peripheral BDNF after acute aerobic exercise (Knaepen et al., 2010, Pilc, 2010, Huang et al., 2014, Dinoff et al., 2017). Szuhany et al. (2015) found a moderate effect size for increases in BDNF following acute exercise and a small yet significant increase in resting BDNF concentrations after chronic exercise training. While the effect of acute exercise on peripheral blood BDNF concentrations appears to be consistent, collectively results highlight the need for further research to establish the relationship between chronic exercise training and resting concentrations of BDNF.

The neuroprotective effects accruing from exercise may be the result of endogenous neurotrophic and nerve growth factors, as well as the proliferation of the receptive cholinergic neurons associated with cognitive performance (Ang et al., 2003). Yet within the literature, some ambiguity remains regarding the effect of chronic aerobic exercise training on basal circulating levels of BDNF, with some studies suggesting increased cardiorespiratory (CR) fitness levels in response to aerobic training leads to increased basal BDNF concentration, while others have demonstrated an inverse relationship or no association (Voss et al., 2011). Relatively brief periods of aerobic training have demonstrated effectiveness at modulating BDNF in both healthy young and clinical populations, increasing its expression at rest (Pereira et al., 2013, Dinoff et al., 2016), as well the magnitude of the effect of an acute exercise bout (Tomporowski, 2003, Dinoff et al., 2017, Szuhany et al., 2015).

A very limited number of studies have examined the interaction between acute and chronic exercise, BDNF and cognitive performance in MCI. Results highlight the need for research into the conditional effects of chronic exercise on basal BDNF concentration and on acute exercise BDNF response. Due to the transient nature of BDNF, there is a need to observe how BDNF responds within the context of structured exercise training and to examine the influence of BDNF relative to cognitive performance over time. The

current study hypothesised that an aerobic exercise (AT) intervention group would demonstrate an increase in basal BDNF concentration and cognitive performance over a 12-week period compared to a balance and toning (BAT) group. It was also predicted that magnitude of change in BNDF in response to acute exercise would increase over time in the AT group in response to training adaptations accrued over time.

7.2 Aims and objectives

The aim of the current study was to examine whether 12 weeks of structured aerobic training had an aggregated effect on resting sBDNF concentration and measures of cognitive performance in an AT and BAT group. The secondary aim was to explore whether chronic aerobic training leads to a greater magnitude of BDNF and cognitive change (pre-post exercise) following an acute bout of exercise. The specific objectives were:

- To measure the effect of a 12-week structured exercise intervention (AT versus BAT) on resting serum BDNF concentration and cognitive performance (visuospatial learning and memory, sustained attention and executive function) and compare between an AT and BAT group
- To explore the BDNF and cognitive response (pre-post) to acute exercise (AT versus BAT) during week 1, 6 and 12 during a 12-week period of structured and supervised AT and BAT exercise training

7.3 Methods

7.3.1 Participant recruitment

Participant recruitment, diagnostic, inclusion and exclusion criteria to all studies presented in this thesis is described in Chapter 2, Section 2.3.2 – 2.3.5. The participants in the current study represent those randomised to the structured one-year AT or equivalent BAT intervention group of the NeuroExercise study.

7.3.2 Study design

This experimental study has a pre-post-test design with measurements taking place pre and post a supervised exercise class during week 1, 6 and 12 of the intervention. As described in Chapter 2, Section 2.3.6, following baseline assessment, participants were randomised to either a 48-week AT (n=19) or BAT (n=22) equivalent. During week 1, 6 and 12 of exercise training, participants completed pre exercise (resting) blood sampling

and cognitive testing (outlined in detail in Chapter 2 Section 2.5). Participants repeated measures of blood sampling (0-10 minutes post completed exercise) and cognitive testing (See Figure 7:1).

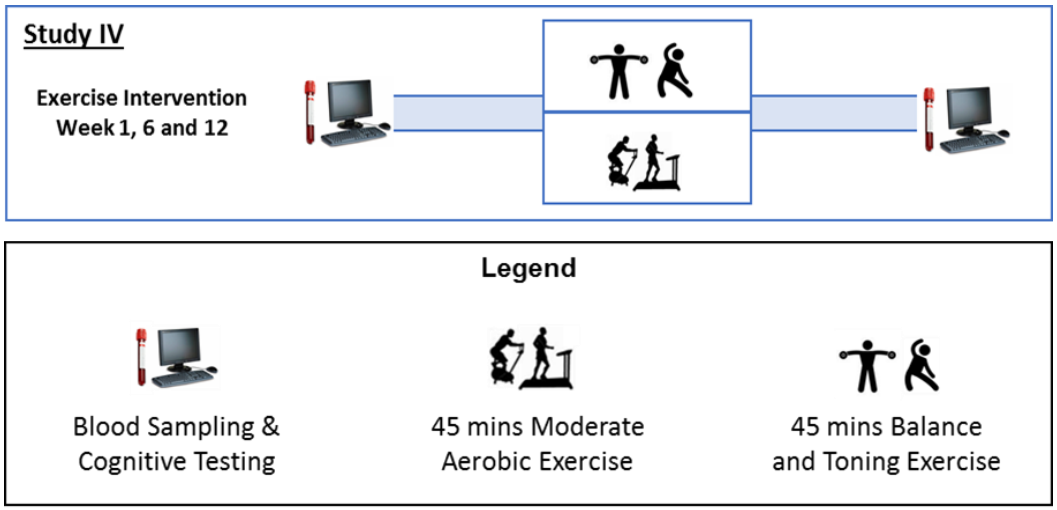

Figure 7:1 Study design outlining study outcomes measures and intervention in Study IV

Outcomes

7.3.3 Blood sampling

Blood samples were collected pre exercise and between 0-10 minutes post the exercise condition. The procedure is outlined in Chapter 2, Section 2.5.1 – 2.5.3.

7.3.4 Cognitive performance

Following blood sampling, cognitive measures were administered pre and post both exercise conditions. These included:

1. CANTAB Paired Associate Learning (PAL) task, a measure of visuospatial learning and memory.
2. Sustained Attention to Response Task (SART), a computerised Go-No-Go paradigm measuring sustained attention
3. Stroop Neuropsychological Screening Test (Stroop) measuring executive function

Testing took approximately 30 minutes to complete. Full details on the psychometric properties and the standardised administration of each cognitive test is outlined in Chapter 2, Section 2.5.5 – 2.5.8.

7.3.5 Intervention

Both exercise conditions (AT and BAT) have been previously described in detail in Chapter 2, Section 2.4.2 and 2.4.3. To summarise, the aim of the exercise intervention was to complete 3 x 45-minute exercise sessions per week. The intervention schedule comprised of supervised twice weekly classes for 8 weeks and once weekly thereafter. Participants completed unsupervised exercise sessions at home as instructed by the study exercise trainer. Participants were instructed to record unsupervised sessions using a home exercise diary. This information was collected and logged by the study exercise trainer each week at the supervised exercise session.

7.3.6 Statistical analysis

SPSS 24 (SPSS Inc; Chicago, IL, USA) was used for analysis with statistical significance set at $p<0.05$. All data are presented as mean ± Standard Deviation (SD) for normally distributed data and median ± Interquartile Range (IQR) for non-normally distributed data. Preliminary analyses were performed to ensure no violation of the assumptions of normality using Kolmogorov-Smirnov test ($p>.05$). Visual inspection of Q-Q plot (to look for systematic deviations) and histogram was performed (to examine skew). Baseline values for all variables were compared between the two groups using an Independent samples t-test for normally distributed data and using a Mann-Whitney U Test for non-normally distributed data. Statistical analysis examined whether participation in regular exercise had an effect on basal BDNF concentration and resting measures of cognitive performance, and if there was any significant difference between the groups over the 12-week training period. To examine the aggregated effect chronic exercise has on the acute exercise change in study outcomes, the change in peripheral BDNF concentration and cognitive performance pre-post a single bout of exercise during week 1, 6 and 12 of exercise training was calculated and compared between exercise groups (AT v BAT). For all study variables, change over time was measured using a repeated measure analysis of variance (ANOVA) test (factor group x time interaction) for normally distributed data and using a Friedman's Test for non-normally distributed data.

7.4 Results

7.4.1 Adherence to exercise intervention

Four participants dropped out of the AT group during the 12-week intervention period (n=2 transport issues, n=2 not interested). Three participants dropped out of the BAT intervention (n=1 transport issue, n=1 orthopaedic surgery, n=1 progression of cognitive

impairment with associated difficulty remembering class schedule). Adherence in the exercise intervention (total number of exercise sessions = number of supervised plus number of unsupervised sessions), including dropouts was 63.9% in the AT group and 70.4% in the BAT group. Adherence to the unsupervised home sessions was lower with 56.9% compliance in the AT group and 46.5% in the BAT group. This represents an overall group adherence of 60.8% in the AT group and 59.8% in the BAT group.

7.4.2 Participant characteristics

Participant demographic and clinical characteristics collected prior to completing exercise condition A included the following: age, sex, education, Montreal Cognitive Assessment (MoCA), Body Mass Index (BMI) and CR fitness level (VO_2max) (Table 7-1). Participants (n=41) had a mean age of 71.4 years (± 5.9), marginally more males to females (23 males, 56.1%); and all were Caucasian (100%). Participants has a tendency towards higher levels of education (13.3 ± 3.6 years) and all participants had MoCA scores within the inclusion criteria range of 18-26 with a mean score of 21.98 (± 2.52). Participants had a mean BMI of 27.49 kg/m2 (± 4.70) and low levels of CR fitness (VO_2max) were prevalent throughout the groups with a mean VO_2max of 19.63 mL/kg/min (± 5.56 mL/kg/min). There was no significant between group differences in baseline participant characteristics. Groups were comparable for baseline BDNF concentrations and measures of cognitive performance.

Table 7-1 Baseline participant characteristics and study variables Study IV. Data are presented as mean ± SD for normally distributed data and as median ± IQR for non-normally distributed data. Note statistical significance; *p < .05. MoCA: Montreal Cognitive Assessment. BMI: Body Mass Index. VO_2max: maximal oxygen uptake. BDNF: Brain Derived Neurotrophic Factor. PALTEA: Paired Associate Learning Total Errors Adjusted. Stroop CWS: Stroop Colour Word Score. SART: Sustained Attention to Response Task. CE: Commission Errors. RT: Reaction Time.

Variable	AT n=19	BAT n=22	p-value
Age (years)	72.42 (5.74)	70.55 (6.18)	0.32
Gender (M/F)	10/9	13/9	0.68
Education (years)	13.42 (3.74)	13.23 (3.66)	0.86
MoCA	21.63 (2.67)	22.27 (2.41)	0.42
BMI (kg/m^2)	27.48 (4.79)	27.49 (4.74)	0.99
VO_2max (mL/kg/min)	19.63 (3.57)	19.62 (6.92)	0.99
BDNF (all) ($pg \cdot ml^{-1}$)	1397.53 (624.07)	1323.75 (539.14)	0.69
BDNF (outliers excl.) ($pg \cdot ml^{-1}$)	1340.81 (593.53)	1261.51 (469.40)	0.65
PALTEA	38.06 (17.44)	36.52 (17.72)	0.74
Stroop CWS	73.82 (29.02)	75.60 (31.14)	0.85
SART CE	2.5 (4)	2 (3)	0.74
SART RT (ms)	103.93 (130.07)	137.05 (66.89)	0.28

7.4.3 Brain Derived Neurotropic Factor

7.4.3.1 The effect of chronic exercise on basal serum BDNF concentration

Resting basal sBDNF concentration measurement, collected pre exercise at week 1, 6 and 12, changed significantly over time (Wilks' Lambda = 0.01, F (2, 19) = 648.99, p=0.000) but did not differ between groups over time (Wilks' Lambda = 0.89, F (2, 19) = 1.14, p=0.34). Resting values (pre exercise) in both groups increased across the three time points with the largest increase in basal sBDNF concentration observed between week 1 (AT: 1340.81 ± 593.53 $pg \cdot ml^{-1}$, BAT: 1261.51 ± 469.40 $pg \cdot ml^{-1}$) and week 6 (AT: 32464.69 ± 6567.70 $pg \cdot ml^{-1}$, BAT: 34418.94 ± 5757.52 $pg \cdot ml^{-1}$) of the exercise intervention (Table 7-2).

Table 7-2 Resting basal serum BDNF concentration during week 1, 6 and 12 of aerobic (AT) and balance and toning (BAT) exercise training. Measurements were collected in a resting state pre exercise during week 1, 6 and 12 of AT and BAT exercise training Data are presented as mean ± SD. Note statistical significance;*p<.05. P-values represent data analysed over time (x time) and as a time-by-group interaction (time x group). BDNF: Brain Derived Neurotrophic Factor.

Variable		Week 1	Week 6	Week 12	p-value x time	p-value time x group
BDNF pg·ml−1						
	AT	1397.53 (624.07)	32462.69 (6567.70)	31091.83 (4789.24)	0.000*	0.75
	BAT	1323.75 (539.14)	33679.80 (6456.59)	30673.57 (3796.79)		
BDNF outliers removed pg·ml−1						
	AT	1340.81 (593.53)	32462.69 (6567.70)	31952.94 (3929.73)	0.000*	0.34
	BAT	1261.51 (469.40)	34418.94 (5757.52)	30673.57 (3796.79)		

7.4.3.2 The effect of chronic exercise training on the acute exercise BDNF response

A one-way repeated measures ANOVA compared the change observed pre-post acute exercise (during week 1, 6 and 12 of the intervention) in sBDNF concentration between study groups (Table 7-3). There were consistent increases observed in sBDNF concentration pre to post exercise across the three time points in the AT group (mean group change pre-post exercise week 1: 165.74 ± 688.04 pg·ml^{-1}, week 6: 1416.19 ± 4992.83 pg·ml^{-1}, week 12: 1493.49 ± 4164.84 pg·ml^{-1}), with an increase also observed in the BAT group at week 12 (mean change pre-post exercise week 1: -115.64 ± 350.73 pg·ml^{-1}, week 6: 76.42 ± 4396.77 pg·ml^{-1}, week 12: 1096.48 ± 3778.57 pg·ml^{-1}). However, despite the observed increase pre-post-acute exercise in the AT group, there was no significant difference in sBDNF concentration change over time (Wilks' Lambda = 0.88, F (2, 17) = 1.14, p=0.34) or between groups over time (Wilks' Lambda = 0.95, F (2, 17) = 0.39, p=0.68).

Table 7-3 The change in serum BDNF concentration pre to post an acute bout of aerobic (AT) balance and toning (BAT) exercise during week 1, 6 and 12 of chronic exercise training. Resting blood samples were collected pre exercise and immediately post exercise during week 1, 6 and 12 of a chronic exercise training. The change in BDNF was calculated by subtracting resting values from post exercise values at each time point. Statistical analysis was performed on the change value to establish if the magnitude of acute exercise BDNF change increased in response to chronic exercise training. Data are presented as mean ± SD for normally distributed data and as median ± IQR for non-normally distributed data. Note statistical significance; *p < .05. P-values represent data analysed over time (x time) and as a time-by-group interaction (time x group). BDNF: Brain Derived Neurotrophic Factor.

Variable		Week 1	Week 6	Week 12	p-value difference x time	p-value difference time x group
BDNF pg·ml−1						
	AT	168.02 (667.57)	1416.19 (4992.83)	1410.30 (3960.73)	0.53	0.77
	BAT	-209.75 (541.91)	168.28 (4291.61)	1096.48 (3778.57)		
BDNF outliers removed pg·ml−1						
	AT	165.74 (688.04)	1416.19 (4992.83)	1493.49 (4164.84)	0.34	0.68
	BAT	-115.64 (350.73)	76.42 (4396.77)	1096.48 (3778.57)		

7.4.4 Cognitive performance

7.4.4.1 The effect of chronic exercise on resting measures of cognitive performance

Pre exercise (resting) cognitive measures during week 1, 6 and 12 were examined to establish if there was a change over time in response to chronic exercise training (Table 7-4). Visuospatial learning and memory performance (PALTEA) remained largely unchanged in both groups (PALTEA AT group week 1: 38.06 ± 17.44, week 6: 38.57 ± 16.22, week 12: 38.00 ± 18.15 and BAT group week 1: 36.52 ± 17.22, week 6: 32.75 ± 17.28, week 12: 36.69 ± 17.96), with no significant change over time (Wilks' Lambda = 0.94, F (2, 26) = 0.82, p=0.44) or group x time (Wilks' Lambda = 0.93, F (2, 26) = 0.93, p=0.39). Performance on the executive function (Stroop) task improved in the AT group from week 6 (74.15 ± 32.42) to week 12 (81.27 ± 29.73) and improved in the BAT group from week 1 (75.60 ± 31.14) to week 6 (83.00 ± 22.40), but showed no significant effect for time (Wilks' Lambda = 0.98, F (2, 21) = 0.16, p=0.84) or group x time (Wilks' Lambda = 0.96, F (2, 21) = 0.36, p=0.70). Sustained attention commission errors remained unchanged in both groups (AT group week 1: 2.5 ± 4, week 6: 2 ±4, week 12: 2 ± 2 and BAT group week 1: 2 ± 3, week 6: 2 ± 3, week 12: 3 ± 3) and did not show any significant change over the 12 week period (commission errors: X^2 (2, n=29) = 3.37, p=0.18). Reaction time demonstrated variability in change within the AT group (week 1: 103.97 ± 130.07 ms, week 6: 135.97 ± 208.92 ms, week 12: 104.20 ± 129.67 ms) and marginally decreased in the BAT group (week 1: 137.05 ± 126.22ms, week 6: 135.99 ± 68.66ms, week 12: 125.13 ± 67.78ms), with no difference over 12 week period (RT: X^2 (2, n=29) = 2.48, p=0.28).

Table 7-4 Resting (pre exercise) cognitive measures during week 1, 6 and 12 of aerobic (AT) and balance and toning (BAT) exercise training. Measurements were collected in a resting state pre exercise during week 1, 6 and 12 of AT and BAT exercise training. Data are presented as mean ± SD for normally distributed data and as median ± IQR for non-normally distributed data. Note statistical significance; *p < .05. P-values represent data analysed over time (x time) and as a time-by-group interaction (time x group). PALTEA: Paired Associate Learning Total Errors Adjusted. Stroop CWS: Stroop Colour Word Score. SART: Sustained Attention to Response Task. CE: Commission Errors. RT: Reaction Time.

Variable		Week 1	Week 6	Week 12	p-value x time	p-value x group
PALTEA						
	AT	38.06 (17.44)	38.57 (16.22)	38.00 (18.15)	0.44	0.39
	BAT	36.52 (17.22)	32.75 (17.28)	36.69 (17.96)		
Stroop CWS						
	AT	73.82 (29.02)	74.15 (32.42)	81.27 (29.73)	0.84	0.07
	BAT	75.60 (31.14)	83.00 (22.40)	80.08 (32.68)		
SART CE						
	AT	2.50 (4)	2.00 (4)	2.00 (2)	0.18	n/a
	BAT	2.00 (3)	2.00 (3)	2.00 (3)		
SART RT (ms)						
	AT	103.93 (130.07)	135.97 (208.92)	104.20 (129.67)	0.92	n/a
	BAT	137.05 (126.22)	135.99 (68.66)	125.13 (67.78)		

7.4.4.2 The effect of chronic exercise training on the acute exercise cognitive response

A one-way repeated measures ANOVA was performed to compare the change pre-post exercise in cognitive measures, between groups during week 1, 6 and 12 of exercise training (Table 7-5). There was no significant difference in visuospatial learning and memory (PALTEA) for time (Wilks' Lambda = 0.91, F (2, 26) = 1.14, p=0.33) or group x time (Wilks' Lambda = 0.97, F (2, 26) = 0.34, p=0.71). Interestingly, the BAT group showed a reduced error rate on the PAL task pre to post exercise at all three time points (mean change pre-post exercise week 1: -4.19 ± 11.27, week 6: -4.30 ± 11.67, week 12: -6.50 ± 13.36). This trend was not observed in the AT group whose performance varied across the three time points. Similarly, executive function (Stroop) showed no statistically significant difference for time (Wilks' Lambda = 0.96, F (2, 21) = 0.36, p=0.69) or group x time (Wilks' Lambda = 0.96, F (2, 21) = 0.40, p=0.67). Although not consistent across all three time points, the AT group increased the number of correct responses on the Stroop interference task pre-post exercise during week 6 and 12 (mean change week 6: 5.92 4.39. ± 12.46, week 12: 2.09 ± 7.67) and the BAT group improved at week 1 and 6 (mean change week 1: 4.39 ± 17.49, week 6: 1.00 ± 14.58). Finally, no significant difference was observed in sustained attention commission errors (X^2 (2, n=29) = 2.76, p=0.25) or reaction time (X^2 (2, n=29) = 0.48, p=0.78) over time. Commission error rate on the SART pre-post exercise remained unchanged in response to exercise over the 12-week period. Reaction time on the SART showed large degrees of variability with no trend observed. Absolute values at all time points are presented in Table X.

Table 7-5 Change in cognitive measures pre-post an acute bout of aerobic (AT) or balance and toning (BAT) exercise at week 1, 6 and 12. The change in cognitive performance was calculated by subtracting resting values from post exercise values at each time point. Statistical analysis was performed on the change value to establish if the magnitude change in cognitive performance increased in response to chronic exercise training. Data are presented as mean ± SD for normally distributed data and as median ± IQR for non-normally distributed data. Note statistical significance; *p < .05. P-values represent data analysed over time (x time) and as a time-by-group interaction (time x group).AT: Aerobic training. BAT: Stretching and toning. BDNF: Brain Derived Neurotrophic Factor. PALTEA: Paired Associate Learning Total Errors Adjusted. CWS: Colour Word Score. SART: Sustained Attention to Response Task. CE: Commission Errors. RT: Reaction Time.

Variable		Week 1	Week 6	Week 12	p-value difference x time	p-value difference x group
PALTEA						
	AT	1.72 (15.42)	-4.79 (8.31)	1.00 (19.04)	0.33	0.77
	BAT	-4.19 (11.27)	-4.30 (11.67)	-6.50 (13.36)		
Stroop CWS						
	AT	-6.00 (18.82)	5.92 (12.46)	2.09 (7.67)	0.69	0.67
	BAT	4.39 (17.49)	1.00 (14.58)	-0.23 (13.65)		
SART CE						
	AT	0.50 (3)	0.00 (3)	0.00 (3)	0.25	n/a
	BAT	0.00 (3)	-1.00 (4)	-1.00 (4)		
SART RT (ms)						
	AT	0.53 (44.48)	-3.48 (56.61)	0.53 (34.85)	0.79	n/a
	BAT	3.76 (31.60)	-3.10 (49.95)	8.55 (35.53)		

7.5 Discussion

This study examined whether participation in 12 weeks of structured exercise training (AT and BAT exercise) changed resting measures of sBDNF concentration and cognitive performance in an MCI cohort. Additionally, the difference in sBDNF and cognitive performance pre-post acute exercise was examined during week 1, 6 and 12 of the intervention and compared between groups. Results indicate that 6 weeks of moderate intensity aerobic or balance and toning exercise performed three times weekly significantly increased resting sBDNF concentration in an MCI cohort. However, the magnitude of change in BDNF following acute exercise did not differ significantly between the two groups across the three time points. Cognitive measures did not change in either the resting or pre-post acute exercise values over time. Results offer tentative support for both AT and BAT exercise interventions for enhancing the BDNF profile in a low fit group of older adults with MCI.

In animal studies, strong evidence supports the role of chronic exercise in upregulating BDNF (Van Praag et al., 1999b, Van Praag et al., 2005, Neeper et al., 1995, Gómez-Pinilla et al., 2002, Vaynman et al., 2004), yet human studies have failed to yield evidence of the same strength. In the current study, an increase in basal sBDNF concentration was observed over time following participation in regular AT and BAT exercise. This increase in resting peripheral BDNF concentration may be reflective of an increase in central BDNF production (Karege et al., 2002, Klein et al., 2011, Pan et al., 1998), although this remains a source of debate (Lanz et al., 2012). Results of the present study agree with several chronic exercise intervention studies that suggest increases in basal levels of circulating peripheral BDNF concentration following aerobic training (Seifert et al., 2009, Zoladz et al., 2008). Seifert et al. (2009) found 3 months of endurance aerobic training significantly increased basal BDNF concentration in a group of young males compared to a control group, but training did not lead to increases in BDNF during exercise. In another group of young healthy males, Zoladz et al. (2008) described a significant within group increase in resting plasma BDNF concentration following 5 weeks of moderate intensity cycling. However, this has not been a consistent finding and a number of chronic aerobic exercise studies have not observed increases in basal circulating BDNF levels (Griffin et al., 2011, Schiffer et al., 2009, Baker et al., 2010c). Schiffer et al. (2009) found no change in basal sBDNF concentration following 12 weeks of aerobic exercise training in a group of university students (Schiffer et al., 2009). Similarly, Griffin et al. (2011) reported that 5 weeks of exercise altered the temporal profile of the serum BDNF response to acute exercise, but did not have any

effect on basal BDNF concentration in a group of healthy young males. Moreover, given that studies discussed herein predominantly included young male participants, generalisability of these findings to cognitively impaired and female populations across the lifespan is limited.

Within MCI cohorts, it has been suggested that chronic aerobic and multimodal type exercise interventions can increase BDNF concentration (Nascimento et al., 2014b, Baker et al., 2010c). Nascimento et al. (2014b) examined the effect of a 16-week multimodal exercise programme in a group of healthy older adults and an MCI group (randomised to training group versus control) and found a significant between-subjects interaction, indicating a training induced improvement on peripheral BDNF concentrations. However, Baker et al. (2010c) reported an increase in peripheral BDNF in males and a decrease in women following a 6-month high intensity aerobic exercise intervention in an amnestic MCI group, suggesting potential sex differences in the BDNF response to chronic exercise. Sex differences in BDNF response to exercise were discussed in Chapter 4, Section 4.5.

Despite a difference in exercise mode, intensity and dose delivered, an increase in basal BDNF concentrations was observed in both study intervention groups. This unexpected finding raises a number of questions. These results suggest that varying modalities of exercise can increase basal BDNF concentration although potential moderating factors should be considered. Within the literature, differences in basal levels of BDNF are not totally unexpected and a number of moderating factors including; age, gender, weight status, diurnal fluctuations, diet and disorders of the metabolic or immunological systems all have an influence on stored and circulating BDNF levels (Lommatzsch et al., 2005, Szuhany et al., 2015). Moreover, in a recent review, exercise interventions consisting of aerobic exercise (defined as >50% of the time) demonstrated greater increases in resting peripheral BDNF concentration (SMD = 0.66, 95% CI: 0.33–0.99, $p < 0.001$) than when studies including all modalities were combined (Dinoff et al., 2016). Furthermore, in a group of older adults with aMCI, significant increases in plasma BDNF levels following 6 months Tai Chi training compared with controls after adjusting for age and gender (Sungkarat et al., 2018), providing tentative evidence that varying modes of exercise have the capacity to increase BDNF. These findings provide preliminary evidence that multicomponent type training (aerobic, resistance, balance and coordination exercises) may also demonstrate an ability to upregulate basal BDNF concentration although further research is necessary to explore this.

Cognitive performance did not differ significantly within or between the study intervention groups over the 12-week period. Despite evidence from studies of human and animal subjects that alterations in BDNF concentration may have functional consequences for cognition, this was not observed in our study cohort. Piepmeier and Etnier (2015) examined correlations between cognition and exercise-induced changes in peripheral BDNF and found significant correlations in studies that included a cognitive measure of memory performance (Winter et al., 2007, Skriver et al., 2014) but not in other cognitive domains (Tsai et al., 2014a, Ferris et al., 2007). An interesting observation in the current study was the improved performance on visuospatial learning and memory task in the BAT group over time while the AT group demonstrated improved performance on an executive function task.

7.6 Conclusion

An increase in basal BDNF concentration was observed after 6 weeks of aerobic and balance and toning exercise intervention in an MCI cohort and this increase was sustained at 12 weeks with continued exercise participation. However, chronic exercise training did not augment the acute exercise BDNF response. Future studies in humans are required to determine whether increases in peripheral concentrations of BDNF reflect central BDNF concentrations and establish if changes in peripheral BDNF concentrations mediate clinical benefits, such as mood and cognition enhancement. This will help establish the clinical relevance of peripheral BDNF as a putative biomarker.

8 Chapter 8: Study V: Peripheral brain derived neurotrophic factor and episodic memory in mild cognitive impairment: results from a one year exercise intervention study

8.1 Introduction

Impairment in episodic memory (the ability to learn and retain new information) is commonly observed in amnestic MCI. Tasks such as CANTAB Paired Associates Learning (PAL) and verbal list learning tasks have been associated with AD biomarkers, hippocampal volume reduction and temporal-frontal network dysfunction (de Rover et al., 2011, Nathan et al., 2017, Greenaway et al., 2006, Ewers et al., 2012). Episodic memory is considered a sensitive factor to discriminate between early and late MCI (Aggarwal et al., 2005, Clément et al., 2010).

A number of studies have demonstrated a positive association between BDNF concentration and cognitive performance in healthy older adults (Gunstad et al., 2008, Komulainen et al., 2008), although this remains a source of much debate. Attenuated loss of BDNF has been reported in MCI cohorts compared to elderly controls and this has shown to correlate with loss of cognitive function, especially in tests of episodic memory (Forlenza et al., 2015, Peng et al., 2005, Yu et al., 2008). However, consensus opinion on the role BDNF plays in the pathogenesis of AD and MCI is equivocal. Due to conflicting findings, there is no definitive consensus regarding the peripheral BDNF profile in neurodegenerative diseases, including MCI populations (Borba et al., 2016).

As MCI represents a prodromal or transitional state between normal age-related cognitive decline and clinical AD, possibilities for early diagnosis and potential treatment are increasing. The American Academy of Neurology's clinical practice guideline on MCI proposes treatment of modifiable risk factors including the recommendation of regular exercise. Physical exercise and higher rates of cardiorespiratory (CR) have demonstrated an ability to increase hippocampal volume in older adults (Erickson and Kramer, 2009a, Erickson et al., 2009) and in MCI populations (ten Brinke et al., 2015, Teixeira et al., 2018). Moreover, preliminary correlational evidence has shown that peripheral measures of BDNF are associated with hippocampal volume and spatial memory in older adult cohorts (Erickson et al., 2010), although this has not been investigated in an aMCI cohort.

The relationship between peripheral serum BDNF concentrations with episodic memory in individuals with MCI is unclear. With the known potential neuroprotective effects of

BDNF, the aim of the current study was to examine resting serum BDNF concentration and tests of episodic memory in a group of older adults with amnestic MCI during the 1 year period of an exercise intervention study. Given the existent literature supporting the efficacy of long-term aerobic exercise in increasing peripheral BDNF and hippocampal volume, it was anticipated that a difference would be observed between the three study intervention groups (Group 1: aerobic exercise (AT); Group 2: non-aerobic balance and toning exercise (BAT); Group 3: control group), with the AT group demonstrating an improved BDNF profile and improved episodic memory compared to the BAT and control group. It was predicted that there would be a difference in CR fitness between the three study groups, with the greatest improvement seen in the AT group.

8.2 Aims and objectives

The aim of this study was to examine serum BDNF concentration and episodic memory in a group of older adults with amnestic MCI over a 1-year period and to investigate whether there was a difference between three intervention groups (AT v BAT v control). The specific objectives were:

- To examine change in resting peripheral serum BDNF (sBDNF) concentration and episodic memory in an amnestic MCI cohort and compare the change in resting sBDNF concentration and episodic memory between three study groups following a one year intervention
- To investigate change in CR fitness (VO_2max) in an MCI cohort over a one year period and explore whether participation in a structured exercise intervention lead to changes in CR fitness compared to a control group

8.3 Methods

8.3.1 Participant recruitment and randomisation

Participant recruitment, inclusion and exclusion criteria to all studies presented in this thesis are described in Chapter 2, Section 2.3.2 – 2.3.5. Following baseline assessment (T0), participants were randomised to one of three arms using a centrally controlled computer generated randomisation list generated by an independent statistician. Participants were randomised to either a 48-week AT (n=19), equivalent BAT intervention (n=22) or to the control group (n=21) as part of the NeuroExerise study.

8.3.2 Study design

This interventional study collected measurements at baseline assessment (T0) and one year later during the study exit assessment (T1) (Figure 8:1).

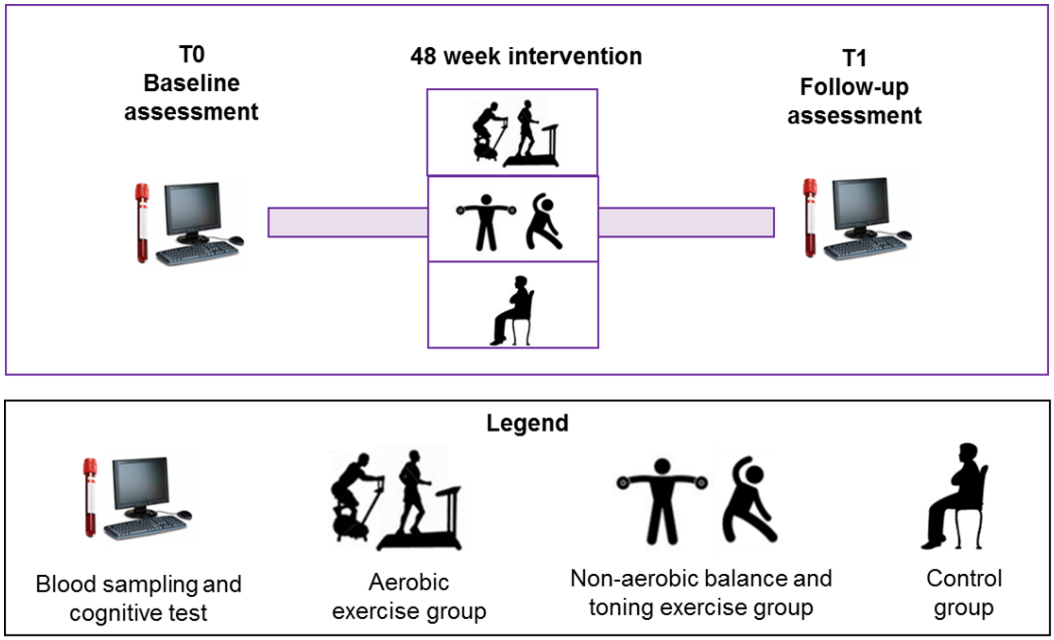

Figure 8:1 Study design outlining study assessments and intervention groups in Study V

8.3.3 Outcomes

8.3.4 Blood sampling

Blood samples were collected in a resting state at both time points. Details on blood sampling procedure are outlined in Chapter 2, Section 2.5.1 – 2.5.3.

8.3.5 Cognitive measures

8.3.6 Episodic memory

Objective cognitive impairment typical of prodromal AD was measured using episodic memory tests.

CANTAB PAL is an episodic memory computer-based task that assesses visual memory and new learning through the testing of conditional learning of pattern-location associations (Strauss et al., 2006). Performance measure of the PAL, the PAL Total Errors Adjusted (PALTEA), refers to the number of times the subject chose the incorrect box for a stimulus on assessment and an adjustment is made for the estimated number of errors they would have made on any problems, attempts and recalls they did not reach. Therefore, the PALTEA value represents the same level attempted for each subject

(Sahakian et al., 1988). As this outcome indicates the number of errors made before the completion of the test, a larger score indicates greater difficulty with the task. Procedure for the administration of the CANTAB PAL is outlined in detail in Chapter 2, Section 2.5.6.

The Cogstate International Shopping List Test (ISLT) is a verbal word list learning test consisting of 3 trials of 12 words and a delayed recall that is administered using a computer (Thompson et al., 2011). The participant is not shown the computer screen or the words. Items for each administration of the ISLT are selected randomly from a pool of 128 words and are presented in the same order across the three trials. Stimuli are presented to the test administrator and read aloud at a rate of one word every 2 seconds. At the completion of each learning trial, participants are asked to recall any words they can remember. Responses are marked by the test administrator on the computer screen. A delayed recall trial is also administered after a delay of 10–15 min with participants asked to recall as many of the words from the list as they could remember.

ISLT is sensitive to the deterioration in memory that is characteristic of prodromal AD, has a standardised test administration and is robust against practice effects (Lim et al., 2013, Thompson et al., 2011). ISLT performance measures used in the current study include:

1. Total free recall = sum of words recalled on Trials 1–3 with a possible value range from 0 to 36
2. Delayed recall score = number of words recalled after a delay with a possible values range from 0 to 12

8.3.7 Global cognition

The Montreal Cognitive Assessment (MoCA), a 10-minute brief screening instrument for the detection of MCI was administered at T0 (version 7.1) and T1 (version 7.3). The MoCA assesses multiple cognitive domains including attention, concentration, executive functions, memory, language, visuospatial skills, abstraction, calculation and orientation (Nasreddine et al., 2005). It is scored out of a maximum of 30 points with a lower score indicating poorer cognitive function.

8.3.8 Cardiorespiratory fitness

A Cardiopulmonary Exercise Test (CPET) was performed on a standard COSMED cycle ergometer and progressed according to the WHO protocol to measure CR fitness (VO_2 max) (Fletcher et al., 2001) as described in Chapter 2, Section 2.4.1.

8.3.9 Intervention

The aim of the exercise intervention groups was to complete 3 x 45-minute exercise sessions per week over a 48 week period as described in Chapter 2, Section 2.3.6.

8.3.9.1 Aerobic exercise condition

The AT condition consisted of a 45-minute bout of moderate intensity exercise as described in Section 2.4.2.

8.3.9.2 Balance and toning condition

The BAT group completed 45 minutes of non-aerobic activities as described in Section 2.4.3.

8.3.9.3 Control group

The control group did not receive any form of exercise intervention but were invited to attend for scheduled study assessments.

8.3.10 Statistical analysis

SPSS 24 (SPSS Inc; Chicago, IL, USA) was used for analysis with statistical significance set at $p<0.05$. All data are presented as mean ± SD for normally distributed data and median ± IQR for non-normally distributed data. Preliminary analyses were performed to ensure no violation of the assumptions of normality using Kolmogorov-Smirnov test ($p>.05$).Visual inspection of Q-Q plot (to look for systematic deviations) and histogram was performed (to examine skew). Baseline values for all variables were compared between the three groups using a one-way Analysis of Variance (ANOVA) for normally distributed data and using a Kruskal-Wallis Test for non-normally distributed data.

The difference in BDNF, episodic memory, global cognition and CR fitness from T0 to T1 was analysed between the three study groups using a one-way ANOVA for normally distributed data and a Kruskal-Wallis test for non-normally distributed data. Change in BDNF, episodic memory, global cognition and CR fitness from baseline (T0) to post intervention (T1) within each group was examined using a paired samples t-test for normally distributed data and a Wilcoxin signed rank test for non-normally distributed data. Pearson product-moment correlation coefficient (r) and Spearman Rank Order

Correlation (rho) were used as appropriate to identify whether ISLT, PALTEA, MoCA or VO_2max were associated with BDNF concentrations.

8.4 Results

Forty-one participants were randomised to an exercise intervention group, n=19 to AT and n=22 to BAT exercise. Six participants dropped out of the study during the intervention period and did not attend for study assessment at T1, (n=2 from the AT group and n=2 from the BAT group and n=2 from the control group). A further five participants dropped out of the exercise intervention but attended for study assessment at T1 (transport issues or not interested AT n=2 and BAT n=1, active orthopaedic issues AT n=1 and BAT n=1).

8.4.1 Adherence to exercise intervention

The mean adherence to the total number of exercise sessions (number of supervised classes and unsupervised home sessions), including those who dropped was 58.5% in the aerobic group (61.8 % to the supervised exercise and 56.3% to the unsupervised exercise) and 50.2% in the BAT group (64.2% to the supervised exercise and 41.2% to the unsupervised exercise). Adherence to the total number of exercise sessions in both intervention groups was as follows: > 60% protocol= 51.2%, > 70% protocol 41.4%, > 80% protocol = 29.2%, >90% protocol = 19.5%.

8.4.2 Participant characteristics

Participant demographic and clinical characteristics collected at T0 are presented in Table 8-1. Participants (n=62) had a mean age of 70.5 years (± 6.3), marginally more females to males (n=33 females, 53.2%); and all were Caucasian (100%). Participants has a tendency towards higher levels of education (13.2 ± 3.2 years) and all participants had MoCA scores within the inclusion criteria range of 18-26 with a mean score of 22.1 (± 2.5). Participants had a mean BMI of 26.8 kg/m^2 (± 4.4) indicating a tendency towards being overweight and had low levels of cardiorespiratory fitness (VO_2max) with a mean VO_2max of 19.26 mL/kg/min (± 5.13). There was no significant between group differences in baseline participant characteristics; age (p=0.20), gender (p=0.11), education (p=0.96), BMI (p=0.26) or method of recruitment. Groups were also comparable for baseline sBDNF concentrations (p=0.15), performance on PAL task (p=0.13), ISLT total correct (p=0.07), MoCA (p=0.63) and cardiorespiratory fitness VO_2max (p=0.74). There was a significant difference in baseline ISLT delayed recall

across study groups X^2 (2, n=61) = 14.42, p=0.001 with the aerobic group (Md 2 ± 4) performing worse than the BAT (Md 5 ± 5) and control group (Md 6 ± 5).

Table 8-1 Baseline participant characteristics and study variables across the three study groups. Data are presented as mean ± SD for normally distributed data and as median ± IQR for non-normally distributed data. Note statistical significance; *p < .05. AT: Aerobic Exercise Group. BAT: Balance and Toning Group. C: Community Recruitment. MC: Memory Clinic Recruitment. MoCA: Montreal Cognitive Assessment. VO2max: Maximal Oxygen Uptake. BDNF: Brain Derived Neurotrophic Factor. PALTEA: Paired Associate Learning Total Errors Adjusted. ISLT: International Shopping List Task.

Variable	AT group n=19	BAT group n=22	Control group n=21	p-value
Age (years)	72.4 (5.7)	70.5 (6.1)	68.8 (6.7)	0.20
Gender (Male / Female)	10 / 9	13 / 9	6 / 15	0.11
Recruitment (C / MC)	6 / 13	11 / 11	9 / 12	0.48
Education (years)	13.4 (3.7)	13.2 (3.6)	13.1 (2.3)	0.96
MoCA	22 (5)	23 (4)	23 (5)	0.63
VO_2max (mL/kg/min)	19.63 (3.57)	19.62 (6.93)	18.54 (4.21)	0.74
BDNF (all) (pg·ml− 1)	9636.06 (9657.62)	3699.52 (6185.86)	5510.54 (7499.13)	0.38
BDNF outliers excl.	9636.06 (9657.62)	3677.04 (4460.05)	4370.47 (5303.29)	0.15
PALTEA	45.56 (16.50)	42.41 (14.13)	37.76 (11.41)	0.13
ISLT Total Correct	14.26 (4.08)	18.09 (5.51)	22.55 (3.34)	0.07
ISLT Delayed Recall	0 (4)	5 (5)	6 (5)	0.001*

8.4.3 Recruitment (memory clinic versus community participants)

There were significant differences in baseline characteristics and study outcomes between those recruited through the memory clinic and those recruited from the community. Differences were observed in age, MoCA, PAL and ISLT with community participants outperforming memory clinic participants (Table 8-2). There was no significant difference in the change observed between these groups over the one year period. Adherence to the intervention (total number of supervised and unsupervised exercise sessions) for memory clinic participants (n=24) was 66.6 classes (± 49.0) and 93.7 (± 40) for participants recruited from the community (n=17), t (39) =-1.87, p=0.06.

Table 8-2 Overall sample by method of recruitment into study (memory clinic versus community recruitment. Overall sample by method of recruitment into study (memory clinic versus community recruitment. Measures of age, education, peripheral BDNF, cognitive performance and cardiorespiratory fitness for both groups. Data are presented as mean ± SD for normally distributed data and as median ± IQR for non-normally distributed data. Note statistical significance; *p < .05

Variable	Memory clinic recruitment n=36	Community recruitment n=26	p-value
Age (years)	71.9 (5.7)	68.5 (6.6)	*0.03
Education (years)	13.2 (3.3)	13.2 (3.1)	0.98
BDNF (all) (pg·ml^{-1})	4994.84 (10546.99)	5037.57 (6245.55)	0.93
BDNF outliers excl.	4658.82 (10563.10)	4400.98 (5265.58)	0.55
MoCA	22 (5)	23 (4)	*0.03
VO_2max (mL/kg/min)	19.11 (3.78)	19.08 (6.02)	0.72
PALTEA	47 (20)	39.5 (21)	*0.008
ISLT Total correct	16.11 (4.65)	21.60 (5.07)	*0.000
ISLT Delayed recall	3.28 (2.19)	6.88 (3.08)	*0.000

8.4.4 Change in BDNF, cognitive function and cardiorespiratory fitness

8.4.5 Brain Derived Neurotrophic Factor

Resting sBDNF concentration increased from 9636.06 pg·ml−1 (± 9657.62) to 24051.24 pg·ml−1 (± 3972.52) in the AT group (p=0.000), from 3677.04 pg·ml−1 (± 4460.05) to 20850.44 pg·ml−1 (± 8623.01) in the BAT group (p=0.000) and from 4370.47 pg·ml−1 (±

5303.29) to 21295.15 pg·ml−1 (± 9958.87) in the control group (p=0.000, however there was no between group difference (F 2,49 = 0.41, p = 0.66).

8.4.6 Cognitive function

8.4.6.1 Episodic memory

Performance on the visuospatial learning and memory (PAL) task improved in both intervention groups with a decrease in error rate from 45.56 (± 16.50) to 42.25 (± 20.86) in the AT group (p=0.59), a decrease from 42.41 (± 14.13) to 34.65 (± 18.96) in the BAT group (p=0.17) and an increased error rate from 37.76 (± 11.41) to 39.22 (± 19.38) in the control group (p=0.78), with no between group difference (F 2,51 = 0.76, p = 0.47). Performance on the ISLT (total correct and delayed recall) remained largely unchanged within all groups. Total correct responses on the ISLT remained static from 14.26 (± 4.08) to 14.82 (± 4.34) in the AT group (p=1.00), from 18.09 (± 5.51) to 18.45 (± 6.27) in the BAT group (p=0.95) and 22.55 (±3.34) to 21.67 (± 4.17) in the control group (p=0.47), with no difference between the three groups (F 2, 52 = 0.17, p=0.84). The ISLT delayed recall increased from 0 (± 4) to 1.5 (± 2) in the AT group (p=0.72), remained unchanged from 5 (± 5) to 5 (± 5) in the BAT group (p=0.46) and increased from 6 (± 5) to 7.5 (± 5) in the control group (p=0.52), with no difference between groups (F 2, 51 = 0.96, p=0.38).

8.4.6.2 Global cognition

MoCA scores (higher scores indicating better cognition) remained unchanged from 22 (± 5) to 22 (± 7) in the AT group (p=0.13), decreased from 23 (± 4) to 22 (± 3) in the BAT group (p=0.20) and increased from 23 (± 5) to 24 (± 4) in the control group (p=0.27), with no between group difference (F 2, 53 = 1.48, p = 0.23).

8.4.7 Cardiorespiratory fitness

CR fitness (VO_2max) increased from 19.63 mL/kg/min (3.57) to 21.35 mL/kg/min (4.33) in the AT group (p=0.08), from 19.62 mL/kg/min (6.93) to 20.83 mL/kg/min (5.52) in the BAT group (p=0.70) and from 18.54 mL/kg/min (4.21) to 20.22 mL/kg/min (4.91) in the control group (p=0.10), however there was no between group difference (F 2, 48 = 0.47, p = 0.62).

Absolute values for each group are presented in Table 8-3.

Table 8-3 Between group differences in study variables at T0 (baseline) and T1 (one year) time points. Data are presented for the aerobic (AT), balance and toning (BAT) and control group as mean ± SD for normally distributed data and as median ± IQR for non-normally distributed data. Note p-value represents within group differences with statistical significance; *p < .05. BDNF: Brain Derived Neurotrophic Factor. AT: Aerobic training. BAT: Balance and toning. BDNF: PALTEA: Paired Associate Learning Total Errors Adjusted. ISLT: International Shopping List Task. MoCA: Montreal Cognitive Assessment. VO_2max: maximal oxygen uptake

Variable	T0: Baseline	T1: Follow up	Difference T0-T1	p-value within group	p-value between group
BDNF pg·ml−1					
AT	9636.06 (9657.62)	24051.24 (3972.52)	12836.09 (9969.90)	*0.000	0.84
BAT	3699.52 (6185.86)	20850.44 (8623.01)	14158.44 (8511.58)	*0.000	
Control	5510.54 (7499.13)	21653.62 (11495.20)	13884.73 (12633.01)	*0.001	
BDNF outliers removed pg·ml−1					
AT	9636.06 (9657.62)	24051.24 (3972.52)	13531.70 (6030.86)	*0.000	0.66
BAT	3677.04 (4460.05)	20850.44 (8623.01)	14600.20 (7845.58)	*0.000	
Control	4370.47 (5303.29)	21295.15 (9958.87)	15751.85 (6990.57)	*0.000	
PALTEA					
AT	45.56 (16.50)	42.25 (20.86)	-2.25 (16.60)	0.59	0.47
BAT	42.41 (14.13)	34.65 (18.96)	-5.95 (18.75)	0.17	
Control	37.76 (11.41)	39.22 (19.38)	1.11 (17.18)	0.78	
ISLT (total correct)					
AT	14.26 (4.08)	14.82 (4.34)	0.00 (3.55)	1.00	0.84

BAT	18.09 (5.51)	18.45 (6.27)	0.05 (3.95)	0.95	
Control	22.55 (3.34)	21.67 (4.17)	0.67 (3.91)	0.47	
ISLT (delayed recall)					
AT	0 (4)	1.5 (2)	-0.44 (2.68)	0.72	0.38
BAT	5 (5)	5 (5)	-0.30 (2.02)	0.46	
Control	6 (5)	7.5 (5)	0.72 (3.35)	0.52	
MoCA					
AT	22 (5)	22 (7)	-0.9	0.13	0.23
BAT	23 (4)	22 (3)	-0.7	0.20	
Control	23 (5)	24 (4)	0.3	0.27	
VO_2max (mL/kg/min)					
AT	19.63 (3.57)	21.35 (4.33)	1.95 (3.88)	0.08	0.62
BAT	19.62 (6.93)	20.83 (5.52)	.50 (5.62)	0.70	
Control	18.54 (4.21)	20.22 (4.91)	1.70 (4.21)	0.10	

8.4.8 Correlation

There was a significant moderate indirect correlation between episodic memory (ISLT total correct and delayed recall) and BDNF concentration at baseline (ISLT total correct: rho=-0.30, n=58, p=0.02 and ISLT delayed recall: r=-0.33, n=55, p = 0.01) and between ISLT total correct and BDNF concentration at T1 (r=-0.29, n=55, p=0.04). At baseline, BDNF did not correlate with PALTEA (rho = .07, p = .59), MoCA (rho = 0.08, p = .54) or VO_2max (rho = 0.03, p = .80).

At baseline, CR fitness (VO_2max) did not correlate with measures of episodic memory (PALTEA: rho= -.04, p = 0.74; ISLT total correct: rho = 0.09, p = 0.46; ISLT delayed recall: rho = 0.11, p = 0.38) or global cognition (rho = -.11, p = 0.39).

8.5 Discussion

This study examined one year change in sBDNF concentration, episodic memory, global cognition and cardiorespiratory fitness in an MCI cohort participating in an exercise intervention study. Results demonstrated a significant increase in resting sBDNF concentration in all study groups over the one year period, with no significant within group change observed in cognitive measures. However, there was no difference between groups (group 1: AT; group 2: BAT; group 3: control) in change in sBDNF concentration, episodic memory, global cognition and VO_2max in a group of older adults with MCI.

Resting sBDNF concentration increased significantly over a one year period across all groups, adding to the existing body of research that has examined the BDNF profile in cognitively impaired cohorts. A number of observational studies have reported higher or equivalent levels of serum BDNF in MCI or AD compared to controls (Angelucci et al., 2010, O'Bryant et al., 2009, Faria et al., 2014, Nagahara et al., 2009). However, contrasting findings have been reported in others that reported reduced BDNF levels in MCI and AD patients compared to healthy controls (Forlenza et al., 2010, Yasutake et al., 2006, Yu et al., 2008, Kim et al., 2015). Given the ambiguity around this topic within the literature, no definitive conclusion can be drawn regarding the role of peripheral BDNF in MCI pathophysiology. One author has postulated that elevated peripheral sBDNF concentration may represent a compensatory repair mechanism in early stages of neurodegeneration, with decreasing BDNF according to the severity of the neurodegeneration and Aβ amyloid accumulation (Laske et al., 2006).

Cognitive measures did not change with 12 months of exercise training. In largely healthy young cohorts, studies have suggested higher BDNF levels may positively effect a number of cognitive processes with improved performance on spatial (Erickson et al., 2009), episodic (Egan et al., 2003), recognition (Komulainen et al., 2008, Whiteman et al., 2014), and verbal memory tasks (Grassi-Oliveira et al., 2008) as well as better hippocampal functioning (Erickson et al., 2012b, Szuhany et al., 2015). Although BDNF can affect hippocampal morphology and function, positive associations with learning and memory have not always been found (Stuart et al., 2014, Kim et al., 2015). While the theoretical evidence for an interaction between chronic exercise, BDNF and cognitive performance is strong, the empirical evidence is weak (McMorris, 2015). In the results of the current study, serum BDNF concentration correlated negatively with episodic memory at both time points, indicating that higher sBDNF concentration was associated with poorer performance on the ISLT task. Furthermore, the significant increase in resting sBDNF concentration over the one year period did not result in any improvement in episodic memory or global cognition. Findings are in agreement with Nettiksimmons et al. (2014) who reported no longitudinal association between sBDNF and cognitive function in older adults. Moreover, a significant difference between memory clinic and community recruits was observed across all cognitive measures at baseline. However, despite these significant cognitive differences, there was no significant difference in resting sBDNF concentration. Much more research is needed in human studies with regard to the effect of acute and chronic exercise on BDNF before any definitive statements concerning its effects on cognition are made.

In the results presented, there was no significant difference between exercise intervention groups and the control group in sBDNF concentration, episodic memory or cardiorespiratory fitness. These findings contrast with previous studies that have examined structured exercise intervention studies in MCI cohorts. An emerging group of studies examining structured multicomponent exercise in MCI have reported significant increases in peripheral levels of BDNF, global cognition, logical and episodic memory (Suzuki et al., 2013, Nascimento et al., 2014b, Teixeira et al., 2018), suggesting that a combination of exercise modalities has more wide-ranging effects on cognitive function over only a single type of exercise (Kirk-Sanchez and McGough, 2014). However, despite the emergence of multi-component exercise, the vast majority of exercise intervention studies to date have focused on aerobic exercise. Aerobic exercise intervention studies have reported improvements in verbal list learning and memory tasks in MCI populations (Nagamatsu et al., 2013b, Carson Smith et al., 2013).

Nonetheless, the evidence is equivocal as not all structured aerobic exercise programmes have demonstrated improvements in episodic memory (Baker et al., 2010c, van Uffelen et al., 2008, Scherder et al., 2005, Tortosa-Martínez et al., 2015). The growing number of studies including neuroimaging and neuro-electric techniques as key outcomes will provide greater insight into the potential structural and functional changes accrued in response to chronic exercise paradigms.

In the aging population, maintaining CR fitness can positively impact on the ability to engage in activities of daily living and on overall health related quality of life (Elavsky et al., 2005, Drewnowski and Evans, 2001, Stewart et al., 2003). Of interest, CR fitness increased across all study groups. The within-group increase observed in the AT group did not reach a statistical significance (AT: M 1.95 ± 3.88 mL/kg/min, BAT: 0.50 ± 5.62 mL/kg/min and control 1.70 ± 4.21 mL/kg/min). Many studies that have shown a positive effect of exercise on hippocampal volume or memory have also demonstrated a measurable change in objective measures of CR fitness (Morris et al., 2017). This implies that in order for exercise to have a detectable effect on the brain, the dose and adherence to exercise need to be sufficient to improve CR fitness. The present study delivered a pragmatic structured one year exercise intervention which was designed with a combination of supervised and unsupervised home exercise training sessions. This resulted in an adherence rate of 51.2% to >60% to the prescribed exercise intervention (total number of completed supervised and unsupervised sessions) and this likely affected overall exercise dose. The adherence is comparable to the findings from Van Uffelen et al. (2007) who reported 63% adherence to a one year exercise programme in an MCI cohort. However, supervised exercise intervention studies in MCI have reported higher adherence rates ranging from 80%-96% (Baker et al., 2010c, De Gobbi Porto et al., 2015, Tortosa-Martínez et al., 2015, Carson Smith et al., 2013) while other studies have completely omitted adherence reporting (Scherder et al., 2005, Wei and Ji, 2014, Varela et al., 2012, Hu et al., 2014). Evidence suggests initiating and adhering to structured exercise is problematic in older adults and those with cognitive impairment (Stiggelbout et al., 2005, Dishman, 1994, Tak et al., 2012). Therefore, strategies optimising adherence support should be considered at the initial study design phase along with novel and more robust methods for reporting exercise dose and adherence (Nilsen et al., 2018). The 1-year follow up period allowed for an observation of BDNF behaviour over time. Furthermore, while MCI is a good predictor of AD its clinical course has demonstrated variability over time in large population-based studies with a number of subjects with MCI reverting to normal cognition. Following the clinical course of

peripheral BDNF and episodic memory in MCI with follow-up at 24 and 36 months would have strengthened the impact of this study.

8.6 Conclusion

A 12-month exercise intervention did not impact BDNF or cognition. This exploratory investigation observed an increase in serum BDNF concentration in an MCI cohort, irrespective of study group (AT, BAT or control). Furthermore, episodic memory did not demonstrate a decline, remaining largely stable over a one year period and this did not differ between study intervention groups. Adherence rates to the prescribed exercise intervention in the current study were poor and future exercise intervention studies need to develop suitable adherence supports to enable active exercise participation in cognitively impaired populations.

9 Chapter 9: General Discussion

9.1 Introduction

The series of studies in this thesis aimed to investigate the effect of acute and chronic exercise on peripheral BDNF concentration, and cognitive performance (visuospatial learning and memory, attention and executive function) in a group of sedentary older adults with MCI. Within the literature, the large number of studies assessing the impact of varying exercise paradigms on concentrations of peripheral BDNF, a putative marker of the exercise induced benefit on brain health, indicates the importance of this topic. Studies within this thesis were designed to allow for a robust exploration of this effect in a cognitively impaired population. Given the assumed modifiable nature of BDNF and the variability of disease progression in MCI, it has been suggested that this population may be amenable to exercise interventions to slow the rate of neurodegeneration through BDNF upregulation. This may also confer a cognitive benefit in this clinical cohort, considered at increased risk of future development of AD or other dementias. Within this thesis, studies addressed the following areas:

Part A: The effect of acute exercise on peripheral BDNF concentration and cognitive performance in an MCI cohort.

- Investigated following a short bout of high intensity aerobic exercise compared to a resting control condition (Study I, Chapter 4)
- Compared two contrasting acute aerobic exercise protocols (short bout high intensity versus longer bout moderate intensity) (Study II, Chapter 5)
- Investigated two distinct acute exercise modalities (moderate intensity aerobic versus non-aerobic balance and toning) (Study III, Chapter 6)

Part B: The effect of chronic exercise on peripheral BDNF concentration and cognitive performance in an MCI cohort

- Examined if 12 weeks of structured training (aerobic and balance and toning) had a cumulative effect on resting measures of peripheral BDNF concentration and cognitive performance and explored whether chronic aerobic training induced a larger acute exercise BDNF and cognitive response (Study IV, Chapter 7)
- Explored peripheral BDNF concentration, episodic memory and cardiorespiratory (CR) fitness in a group of older adults with MCI over a 1-year exercise intervention period and investigated whether there was a difference between three

intervention groups (aerobic exercise v balance and toning v control) (Study V, Chapter 8)

The studies contained within this thesis are timely given the continually evolving science around exercise and brain health. In 2016, the Global Council on Brain Health (GCBH) issued recommendations on physical activity and brain health for people as they age (Global Council on Brain Health, 2016). However, this report highlighted that current international public health guidelines are based on cardiovascular research a number of gaps within the research remain pertaining to clinical populations. The studies within this thesis will fill knowledge gaps related to understanding the impact of duration, intensity and different types of exercises on BDNF and cognitive performance. As the implications of individual results have been discussed in previous chapters, the present section will provide a succinct analysis of the key points regarding the relationship between acute and chronic exercise, peripheral BDNF concentration, cognitive performance and CR fitness in an MCI population.

9.2 Analysis of key points

9.3 Acute exercise and BDNF

The first set of analyses demonstrated the upregulation of serum BDNF concentration following a short bout of high intensity exercise compared to a 30-minute resting control condition (Study I, Chapter 4). The observed BDNF increase is in agreement with existing meta-analytic reviews (Dinoff et al., 2017, Szuhany et al., 2015, Knaepen et al., 2010, Huang et al., 2014) and numerous experimental studies (Ferris et al., 2007, Griffin et al., 2011, Vega et al., 2006, Winter et al., 2007, Tsai et al., 2014b, Tonoli et al., 2015, Tang et al., 2008, Hwang et al., 2016, Hötting et al., 2016) on this topic, which have consistently supported a transient upregulation of peripheral BDNF following an acute bout of high intensity aerobic exercise. However, a large number of these studies have included healthy young and predominantly male cohorts, thereby limiting the generalisability of findings to older cognitively impaired populations who may present with underlying BDNF related neuropathology. However, two recent studies have been published which examined the acute exercise-BDNF response in MCI (Tsai et al., 2018) and AD cohorts (Coelho et al., 2014). Tsai et al. (2018) found that an acute bout of 30 minutes of moderate intensity aerobic exercise significantly increased sBDNF levels in a group (n=25) of older adults with amnestic MCI. Similarly, in a group of older adults with early AD (n=21), Coelho et al. (2014) reported increases in BDNF plasma levels following

a high intensity graded exercise protocol. In agreement, findings in the present study indicate that older adults with MCI, despite being in the early stages of the neurodegenerative process, retain the ability to increase peripheral BDNF concentration following acute high intensity aerobic exercise. The present work adds to an expanding body of evidence supporting acute exercise as a non-pharmacological treatment strategy for upregulating peripheral BDNF concentration.

In contrast to Study I, BDNF did not change significantly in response to exercise during the testing conditions applied in Study II or Study III. In Study II, two contrasting acute aerobic exercise protocols (short bout high intensity versus longer bout moderate intensity) were compared. In this study BDNF showed only marginal change, with a decrease (-4.58%) following a short bout of high intensity exercise and an increase (4.99%) following a longer bout of moderate intensity exercise. Study III examined the difference between two distinct exercise modalities (moderate intensity aerobic versus non-aerobic balance and toning). In these results, BDNF increased (50.3%) following 45 minutes of moderate intensity exercise and slightly decreased (-3.8%) following 45 minutes of balance and toning exercise. However, Study I had a stronger study design, included randomisation and was sufficiently powered on the primary outcome (BDNF) while study II and III were likely underpowered and considered exploratory in nature. Taken collectively with consideration to study design limitations, results support the efficacy of acute aerobic exercise (short bout of high intensity exercise and 45 minutes moderate intensity exercise) in increasing peripheral BDNF immediately post exercise.

9.4 Chronic exercise and BDNF

Study IV (Chapter 7) demonstrated that 6 weeks of moderate intensity aerobic or balance and toning exercise, performed three times weekly, resulted in a significant increase in basal sBDNF concentration in an MCI cohort. This finding suggests that a relatively short period of exercise training can induce changes in basal BDNF concentration. Since BDNF is generally considered to be lower in individuals with neurodegenerative disorders (Phillips et al., 1991, Yasutake et al., 2006), an increase in BDNF via exercise may confer a clinical benefit by ameliorating this abnormality.

An increase in basal BDNF concentration following structured chronic aerobic exercise has been reported within the literature (Seifert et al., 2009, Zoladz et al., 2008, Voss et al., 2013). Across studies in this thesis, the BAT group was designed as a non-aerobic

exercise group, and in line with existing literature, it was not anticipated to observe a comparable degree of peripheral BDNF upregulation in this group (Voss et al., 2013, Baker et al., 2010c). Nonetheless, it could be postulated given the overall sedentary low-fit status of study participants, that the BAT exercise (yoga, light resistance exercise, stretching, balance, coordination, relaxation, group games) may have provoked intermittent physiological responses similar to low - moderate intensity exercise. The BORG Rate of Perceived Exertion (RPE), a recognised subjective marker of exercise intensity was used to monitor intensity in this group, with a target of ≤ 10 (Borg, 1998). However, the American College of Sports Medicine (ACSM) has suggested that there is insufficient evidence to support using the RPE as a primary method of exercise training (Garber et al., 2011). On reflection, polar heart rate monitors which are used to prescribe aerobic exercise intensity may have been useful in this non aerobic group to ensure that aerobic stimulus remained low while completing these non-aerobic tasks (Achten and Jeukendrup, 2003).

In the results presented in Study IV (Chapter 7), chronic exercise training did not increase the magnitude of BDNF change with acute exercise. Although acute aerobic exercise (45 minutes moderate intensity) appeared to deliver a consistent upregulation of BDNF pre-post exercise, the magnitude of this increase was not statistically significant over time. Griffin et al. (2011) reported that 5 weeks of aerobic exercise training altered the temporal profile of the serum BDNF response to acute exercise in healthy young males. It has been suggested that exercise upregulation of BDNF may enhance the sensitivity of downstream signalling cascades and chronic exercise training may prime the system so that BDNF levels are quickly restored with subsequent exercise, promoting neuronal adaptations (Lista and Sorrentino, 2010, Sleiman et al., 2016). Functional (neuroelectric) and structural measurement techniques were beyond the scope of the current body of work, but would have been of added value to establish if neural training adaptations occurred over time.

In this thesis, an increase in resting basal peripheral BDNF concentration was observed across all three study groups over the 1 year intervention period (Study V, Chapter 8). It is difficult to draw direct comparisons to the existing observational studies on this topic in MCI cohorts which have largely compared resting peripheral BDNF concentration in MCI and AD cohorts to healthy controls. However, the increase observed within the study cohort over time may represent a transitional phase in the underlying MCI disease process (Laske et al., 2006, Angelucci et al., 2010, Nagahara et al., 2009). As outlined

in the Chapter 1, research regarding the diagnostic and prognostic value of resting peripheral BDNF concentration in MCI has been inconsistent. The results observed in this thesis lend support to the hypothesis of an increase in peripheral BDNF during the clinical course of MCI (Angelucci et al., 2010, Laske et al., 2006, Faria et al., 2014). Conversely, a meta-analytical review and a number of observational studies have found peripheral BDNF to be significantly reduced in MCI and AD patients compared to healthy controls (Lee et al., 2009, Qin et al., 2017, Yu et al., 2008). This evidence is further corroborated by a post mortem study that used grey matter from parietal cortex samples (Peng et al., 2005) and another that used cerebrospinal fluid to measure BDNF (Forlenza et al., 2015), with both studies reporting reduced BDNF in AD and MCI compared to healthy controls. On weight of the existing evidence, lower BDNF in MCI compared to cognitively normal controls is supported to a greater extent within the literature, although further research is still needed to confirm this hypothesis.

9.5 Cardiorespiratory fitness and BDNF in MCI

Physical activity and fitness levels are known to decline across the lifespan (Troiano et al., 2008, Betik and Hepple, 2008) and these deficits are amenable to exercise interventions (Dunn et al., 1999). In the initial part of this work (systematic review presented in Chapter 3), the lack of valid and reliable objective measures of cardiorespiratory fitness (CR) was highlighted as a gap that needed to be addressed within exercise intervention studies in MCI, to allow for an accurate exploration of the intervention effect on this key outcome. A strength of the work contained within the current thesis was the measurement of cardiorespiratory fitness by Cardiopulmonary Exercise Testing (CPET). CPET measuring maximal oxygen uptake (VO_2max) is considered the gold standard in the objective measurement of CR fitness (Agnew, 2010, Wasserman et al., 2005). It was apparent from the baseline CPET results in Study I (Chapter 4), that CR fitness is suboptimal in this patient cohort. In the work presented, baseline CR fitness was compared to age and gender norms and participants presented as very poor (< 20^{th} percentile) in 85.5% (n=53) of the overall study group, with a further 8.1% (n=5) categorised as poor (20^{th} – 40^{th} percentile).

While this provides justification for strategies aimed at addressing this modifiable deficit, the one year intervention of the current study did not achieve this outcome and will be discussed below. Within the literature, many studies that show a beneficial effect of exercise on hippocampal volume or cognition simultaneously demonstrate a measurable

change in objective measures of CR fitness (Morris et al., 2017, Colcombe and Kramer, 2003a, Reiter et al., 2015). Disappointingly, at one year follow-up, there was no significant difference in CR fitness (VO_2max) within or between study groups, which may account for the lack of any measurable cognitive improvement over the 1 year period. In Study V, it was reported that CR fitness (VO_2max) increased from 19.63 mL/kg/min (3.57) to 21.35 mL/kg/min (4.33) in the AT group (p=0.08), from 19.62 mL/kg/min (6.93) to 20.83 mL/kg/min (5.52) in the BAT group (p=0.70) and from 18.54 mL/kg/min (4.21) to 20.22 mL/kg/min (4.91) in the control group (p=0.10). CR fitness was a key target outcome as low CR fitness has been linked to poorer cognition amongst a host of other poorer health outcomes (Wendell et al., 2014). It is considered an important index of health, a strong predictor of cardiovascular and all-cause mortality, and health related quality of life (Myers et al., 2015, Leeper et al., 2013). The failure of the exercise intervention to significantly increase CR fitness in the AT group is not entirely surprising given the issues with adherence which affected the overall exercise volume delivered. Issues relating to exercise intervention adherence and the implications of this will be discussed later in this chapter.

9.6 Acute exercise and cognitive performance

The findings of the work contained within this thesis does not support a beneficial effect of acute exercise on cognitive performance in MCI. Acute bouts of exercise have generally demonstrated transient improvements in cognitive performance, with several published studies and reviews investigating the dose–response relationship between aerobic exercise intensity and cognitive performance after exercise (Ekkekakis and Petruzzello, 1999, Brisswalter et al., 2002, Lambourne and Tomporowski, 2010, Chang et al., 2012, Ferris et al., 2007, McMorris and Hale, 2012, Tomporowski, 2003, Kamijo et al., 2007, Basso et al., 2015). One major drawback in interpreting existing literature is that it has primarily been conducted in cognitive normal cohorts. To date, only two studies have investigated the effect of acute exercise on cognitive performance in MCI (Tsai et al., 2018, Segal et al., 2012). Under similar exercise conditions to the aerobic exercise conditions contained within this thesis (Chapter 4-6), these studies demonstrated only modest cognitive improvement on retrograde memory task and in reaction time on the Flanker (executive function) task. While no significant cognitive improvements were noted following acute exercise across studies I-III (Chapter 4-6), an important observation was that cognitive performance did not deteriorate, which suggests no negative impact of acute exercise on cognitive performance.

Primary analyses did not establish a measurable effect of acute exercise on cognitive performance. In the secondary analysis in Study I (Chapter 4), improved performance on an executive function (Stroop) task was observed within group B (T1: baseline, T2: post resting control condition, T3: post short bout high intensity exercise) over time. Post hoc analysis revealed a significant increase in Stroop CWS from pre exercise T1 (M = 75.25 ± 26.97) to post exercise T3 (M = 83.93 ± 21.47) (mean increase = 8.67, 95% confidence interval 13.55 to 3.80), (p=0.001, ES .34). These within group findings are supported in acute exercise studies that have also utilised the Stroop paradigm as a measure of executive function (Sibley et al., 2006, Yanagisawa et al., 2010). Moreover, given the strong associations reported between CR fitness and executive function in older adults (Hayes et al., 2014, Kawagoe et al., 2017), it could be hypothesised that the significantly higher CR fitness that was observed in group B in Study I, may have contributed to the changes in an executive function task observed within this group. Given these preliminary findings, an interesting direction for future acute exercise-cognitive studies in MCI populations would to be to stratify groups by fitness category to establish if CR fitness moderates the acute exercise-cognitive relationship.

The cognitive response to acute exercise is modulated by a number of characteristics described previously in this thesis (Brisswalter et al., 2002, Tomporowski, 2003, Lambourne and Tomporowski, 2010, Chang et al., 2012, McMorris and Hale, 2012, McMorris, 2015). One moderator variable that may be particularly relevant to the current work, is the timing of the cognitive task relative to exercise. Findings from a number of meta-analyses have suggested an optimal time window post exercise during which the effect of acute exercise on cognitive performance is greatest. This timeframe varies considerably from 11 – 48 minutes (Hillman et al., 2009), with the majority suggesting 11-20 minutes post exercise as the optimal window for observing a cognitive effect (Lambourne and Tomporowski, 2010, Chang et al., 2012). It is possible that the timing of the cognitive tasks performed between 5-40 minutes post-exercise across all acute exercise studies exceed this timeframe, and may partially explain the null effects reported.

9.7 Chronic exercise and cognitive performance

Despite preliminary evidence that exercise training may improve cognition in MCI (Baker et al., 2010c, Gauthier et al., 2006, Lautenschlager et al., 2008, Smith et al., 2013b),

cognitive performance in Study IV (12 weeks AT v BAT) and V (1 year AT v BAT v control) did not differ between study groups following chronic exercise training. Results of the systematic review reported in Chapter 3 revealed a small body of emerging evidence, that structured purposeful aerobic exercise of moderate intensity performed for six months demonstrated improvements in cognitive performance in areas of global cognition, memory and executive function in people with MCI (Baker et al., 2010c, De Gobbi Porto et al., 2015, Gill et al., 2015, Nagamatsu et al., 2013b, Wei and Ji, 2014, Hu et al., 2014). Cognitive domains of attention, processing speed and visuospatial skills did not appear amenable to chronic exercise induced change (De Gobbi Porto et al., 2015, Gill et al., 2015, Sacco et al., 2015, Carson Smith et al., 2013, Tortosa-Martínez et al., 2015, van Uffelen et al., 2008, Scherder et al., 2005). In contrast to the findings of the systematic review, global cognition (MoCA), memory (episodic memory – PAL and ISLT) and executive function (Stroop) did not change between study groups following a 1-year exercise intervention. A possible explanation for the lack of a cognitive effect may be the poor adherence rates in the current study which were lower than adherence rates of studies included in the systematic review (Chapter 3).

Despite a rigorous randomisation protocol in the NeuroExercise Study, there were significant differences in baseline ISLT delayed recall (episodic memory) across study groups, with the AT group performing worse than the BAT and control group. These baseline differences suggest the AT group presented with a higher degree of cognitive impairment at baseline, which may have been more representative of late stage MCI. Importantly, episodic memory and global cognition did remain stable over the one year period across all study groups and a number of factors may have contributed to this. At baseline, the present study cohort presented with relatively high levels of education (n=38, 59.4% >13 years education). Research has demonstrated that high levels of education attainment are associated with resilience against age-related or pathology-related impairment of cognitive function (Stern, 2012), suggesting high education may have served as a protective factor. Furthermore, the BAT group, designed to act as an active control were given equivalent opportunity for group and social interaction in supervised exercise classes. Social interactions have important intrinsic cognitive components and promote cognitive engagement which may have contributed to overall cognitive enhancement in this group (Seeman et al., 2001).

Despite limited high quality exercise intervention trials in MCI, the American Academy of Neurology's recently updated its guideline on overall MCI management includes the

recommendation for regular exercise as part of the overall approach to disease management. Despite a growing research base on this topic, this recommendation was based on 2 studies (Nagamatsu et al., 2012, Suzuki et al., 2013). In a single blinded RCT, 86 community-dwelling women aged 70–80 years with MCI were randomised to twice-weekly resistance or aerobic exercise or to a control group for 26 weeks (Nagamatsu et al., 2012). The resistance training group showed significantly improved results on executive function (Stroop test) and associative memory tests compared to the balance and toning group. In a randomised single-blind trial comparing a multicomponent exercise program (90 min, 2/weekly, for 6 months) to an education control group (2 education classes), Suzuki et al. (2013) found MMSE scores differed at end of study between intervention groups in those with aMCI. Adherence rate in these studies was 89% and 94% respectively. A number of contrasts exist between these studies and the present study, including the utilisation of resistance exercise and multicomponent training. The broad range of available exercise modalities can provoke varying physiological and biological responses (Hawley et al., 2014, Zhang et al., 2018) and resistance exercise in particular has demonstrated an ability to enhance cognitive function through different pathways and mechanisms (Liu-Ambrose et al., 2010, Nagamatsu et al., 2012, Best et al., 2015, Chang and Etnier, 2009). These findings suggest the need for future intervention studies to diverge from isolated aerobic training and consider the inclusion of multicomponent (aerobic, resistance and balance and coordination) interventions for exercise induced cognitive change.

While exercise appears to have a neuroprotective effect in cognitively intact adults and reduces risk for future MCI or dementia (Sofi et al., 2011, Geda et al., 2010), the ambiguity regarding the role of chronic exercise training in facilitating cognitive improvements in MCI, AD and beyond continues. It is important to bear in mind that exercise produces significant social, physical, and functional benefits for people with MCI and dementia irrespective of the effect on cognition. These health-related benefits cannot be overlooked for their importance in enhancing overall health related quality of life (Panza et al., 2018, Pa et al., 2014).

9.8 Critical Analysis

This thesis contained a number of studies that were designed to examine the interaction between acute and chronic exercise, BDNF, cognitive performance and CR fitness in an MCI cohort. It is important to analysis the limitations of the studies contained within this

body of work. As a number of limitations were common across all studies in the thesis, they will be summarised here.

9.8.1 Study sample

One strength of studies within this work was that a unique population, a sedentary low fit MCI group considered a high-risk group for future cognitive decline were recruited. Well-validated MCI diagnostic criterion were rigorously applied (Albert et al., 2011). Previous studies have used variations in definitions of MCI and its subtypes, which introduces a large degree of variability in study populations and makes comparisons among studies difficult.

Across studies, convenience and self-selection sampling methods were used which are not without limitations. Participants were recruited though established memory clinics due to the ready availability of a suitable population. Participants recruited from community advertisements self-selected into the study, which introduces inherent bias into the sample. A self-selecting population in a cognitive based study is likely to be biased towards high-functioning, well-educated and motivated volunteers (Nebes et al., 2006), which may limit the generalisability of our results to less-educated populations.

Although established MCI diagnostic criteria were applied, the two study recruitment pathways (memory clinic versus community) produced a heterogeneous sample of participants with amnestic MCI. This was evident through the significant differences observed in baseline age, measures of global cognition and episodic memory between the groups, with participants recruited from the community significantly outperforming their memory clinic counterparts. Episodic memory in particular, is considered a sensitive factor to discriminate between early and late MCI (Aggarwal et al., 2005, Clément et al., 2010). It is therefore plausible that those recruited from memory clinics presented with late stage MCI and those recruited from the community represented early stage MCI. While individuals with aMCI are known to have variable rates of progression to dementia and AD (Farias et al., 2009), there was no significant difference in the change in episodic memory or global cognition between memory clinic and community recruits over the one year period.

9.9 Adherence

In Study IV and V, a chronic structured exercise intervention was examined. Adherence to the structured exercise intervention (total number of supervised and unsupervised exercise sessions) demonstrated variable rates with an overall low compliance. The mean adherence (total number of supervised and unsupervised exercise sessions), including exercise intervention and study dropouts in the AT group was 58.5% (61.8 % to the supervised exercise and 56.3% to the unsupervised exercise) and 50.2% in the BAT group (64.2% to the supervised exercise and 41.2% to the unsupervised exercise). Evidence suggests initiating and adhering to structured exercise is problematic in older adults and for those with cognitive impairment (Stiggelbout et al., 2005, Dishman, 1994, Tak et al., 2012). Adherence to the intervention (total number of supervised and unsupervised exercise sessions) for memory clinic participants (n=24) was 46.2% (± 34.0%) and 65.0% (± 27.7%) for participants recruited from the community (n=17). Given the higher adherence to the exercise intervention observed in the community recruits, it may be suggested that those recruited to exercise programmes from memory clinics present with late stage MCI and by proxy present with more significant cognitive impairment. This late MCI subgroup that emerged within the current study may have required greater adherence support to assist with participation in a structured exercise intervention.

Converging evidence suggests self-efficacy may operate as one possible mediator linking psychosocial influences to positive health functioning such as regular habitual exercise (Salovey et al., 2000, Garcia and King, 1991). In structured exercise programmes, a supportive cohesive group dynamic facilitates development of self-efficacy beliefs among participants and may be a promising intervention tool in the promotion of exercise adherence (Christensen et al., 2006). Establishing group cohesion can be conditioned by the social composition of the group, the teaching ability by the instructor, and the exercise activities. Given the issues with adherence observed in Study IV and V in this thesis, there clearly remains a multitude of unanswered questions concerning the design of exercise interventions in MCI. Increasing knowledge around patients' perceived barriers, reasons for non-adherence to exercise and drop-out may provide guidance to and aid in the design of successful strategies to increase participation and develop suitable and sustainable supports to facilitate exercise participation in MCI.

Across study sites in the NeuroExercise trial, the model of exercise programme delivery was found to have some differences. This may have affected adherence rates to the exercise intervention as exercise classes at the Dublin site were carried out exclusively in an acute hospital setting. Programme design is an important consideration in facilitating adherence of participants (Farrance et al., 2016). In the NeuroExercise multi-site trial, a number of challenges were encountered with varying trial recruitment and retention rates across sites. Analysis of recruitment and retention rates found that the non-medical sports university site (German Sports University Cologne), which provided free access to a large range of exercise groups in a community-based sports environment, proved a more successful strategy than recruitment from memory clinics and delivery of the exercise intervention in a hospital setting (Sanders et al., 2018). These findings indicate that exercise delivered in a non-stigmatising community-based setting, rather than a hospital based medical setting may be an important factor in recruitment and exercise adherence in subjects with MCI. Relating these findings to a local context would suggest that the numerous established exercise groups in the community may be best placed to deliver exercise in this population.

9.10 Considerations in BDNF analysis

Findings of the current work supports the hypothesis that peripheral BDNF concentration is increased after a short bout of high intensity exercise and after six weeks of AT or BAT training. However, there are some limitations in BDNF measurement that should be considered. Firstly, only one measurement of BDNF was collected immediately post exercise to capture exercise induced change. This timeframe did not facilitate a time-course observation of BDNF but was considered most appropriate as BDNF returns to pre exercise baseline values between 10 – 50 minutes post exercise (Schmidt-Kassow et al., 2014, Tang et al., 2008, Ferris et al., 2007). Secondly, peripheral measurement of BDNF is not without limitations, as processes occurring centrally in the brain may not have a measurable influence on peripheral blood markers; nor may circulating BDNF have any influence on brain function within the timeframe of experimental conditions in this thesis. BDNF secretion in the central nervous system is thought to contribute to the amount of circulating peripheral BDNF levels (Lommatzsch et al., 2005). While animal studies have demonstrated a high correlation between peripheral and central BDNF concentrations (Karege et al., 2002) evidence in human studies is lacking (Pillai et al., 2010). The human blood brain barrier is considered by some to be structurally and functionally different from animal models, therefore it cannot be inferred from animal models that BDNF can cross the human blood brain barrier (Poduslo and Curran, 1996,

Pan et al., 1998). Thirdly, the source and roles of BDNF in the periphery are not well established with suggestions that serum BDNF protein is stored in immune cells, endothelial cells and vascular smooth muscle cells or platelets and is released upon agonist stimulation (Fujimura et al., 2002, Rosenfeld et al., 1995). Finally, while the general consensus is that BDNF may represent an important measurable biomarker, the poor reproducibility of BDNF measures has to date prevented its validation for clinical purposes. Concerns have been expressed regarding the inter-assay variability of BDNF measurement (Polacchini et al., 2015). However, serum is generally considered the preferred and more reliable choice of blood sample for BDNF measurement since BDNF concentration in plasma is affected by handling of the blood sample due to the presence of platelets, which store BDNF and upon degranulation secretes BDNF (Elfving et al., 2010, Radka et al., 1996, Fujimura et al., 2002).

Differences in basal levels of BDNF are not totally unexpected and may relate to a number of factors including; age, sex, diurnal fluctuations, diet, and disorders of the metabolic or immunological systems (Szuhany et al., 2015, Knaepen et al., 2010). Furthermore, a number of pharmacological treatments commonly prescribed in older adults are known to alter BDNF levels. Of particular relevance, acetylcholinesterase inhibitors, occasionally prescribed in MCI are known to increase serum BDNF levels (Leyhe et al., 2008). In addition, depressive symptoms are commonplace in MCI with a reported incidence of 36% (Modrego and Ferrández, 2004, Lyketsos et al., 2002). Antidepressant drugs are also known to increase serum BDNF concentration (Wilson et al., 2008, Schmidt and Duman, 2007, Castrén and Rantamäki, 2010).

Other factors that may mediate BDNF response to exercise were beyond the scope of the current work. The BDNF val66met polymorphism, a genetic variant that occurs in 33% of the population, is strongly associated with decreased levels of BDNF secretion (Egan et al., 2003), and the degree of cognitive impairment in MCI (Nagata et al., 2012). Furthermore, Apolipoprotein E (APOE) gene ε4 allele, the most prevalent genetic risk factor for late onset AD affects the expression of BDNF (Allard et al., 2017), alters susceptibility to neuropathology and may be an important considerations in understanding responders to exercise (Leckie et al., 2014, Erickson et al., 2013, Watts et al., 2018, Hopkins et al., 2012, Nascimento et al., 2014c). Although beyond the scope of the current study, these are important considerations for future studies to help expand our understanding of variations in individual differences in acute and chronic exercise effects (Canivet et al., 2015).

9.10.1 Blood sampling

Circadian rhythms generated by the suprachiasmatic nucleus, represents an endogenous biological clock in the hypothalamus that regulates the daily timing of many physiological and behavioural rhythms (Klein et al., 1991). Emerging research suggests that peripheral BDNF concentrations fluctuate with circadian rhythms (Drakopoulos et al., 2015, Begliuomini et al., 2008, Pluchino et al., 2009). Due to logistical and practical issues around study scheduling, blood samples across all studies within this thesis were collected in a non-fasting state between 8-3pm. As this time was not standardised, it may have resulted in large degrees of variability in BDNF measures. Therefore, the potential influence of diurnal variation in the BDNF results cannot be ruled out. Future studies should aim to collect samples at a standardised time point to overcome this potential bias.

9.11 Cognitive testing

In the current work, validated neuropsychological tests were chosen in collaboration with a neuropsychologist and based on sound theoretical justification. Study V measured episodic memory impairment (i.e., the ability to acquire and retain new information), which is of particular relevance to an amnestic MCI population that presents with this as the primary cognitive deficit.

One weakness in design across studies was that the order of cognitive tasks (1. PAL; 2. Stroop; 3. SART) was not counterbalanced, a technique used in research to deal with order effects when using a repeated measures design that avoids the introduction of confounding variables. Furthermore, MoCA versions (7.1 and 7.3) were not counterbalanced at T0 and T1 in Study V (Chapter VIII). Some authors have argued that different items on MoCA may not be of comparable difficulty to their corresponding originals of similar content (Lebedeva et al., 2016). In Study I (Chapter IV), secondary analysis of change in cognitive performance (group B) demonstrated improvement in executive function post exercise. However, group B completed an additional measurement of cognitive measures (T3), thereby increasing the risk of type I error due to practice effects of repeated tests which may be an important confounder of these results (Goldberg et al., 2015).

9.12 Exercise conditions

The experimental exercise conditions represented well defined, contrasting acute exercise paradigms and were performed and supervised in a controlled and structured testing environment. However, in Study II (Chapter 5), the mode of aerobic training was not standardised across conditions. Condition A was performed exclusively on a stationary bike while condition B comprised of a combination of stationary bike, treadmill walking, and elliptical training. Exercise mode has been independently related to the size of the overall effect, with larger effect sizes associated with ergometer cycling than with running protocols (Lambourne and Tomporowski, 2010).

It has previously been shown that control groups in studies where intervention assignment cannot be concealed from the study participants, such as is the case with exercise interventions, compensatory behaviours can be expected. Although participant in the control group were not given any advice or guidance regarding exercise, participants in this group may have increased overall physical activity levels over the study intervention period. Although beyond the scope of the current thesis, this will be analysed in objective actipraphy measurement in the NeuroExercise Study.

9.13 Potential bias

As the majority of work contained within this thesis was performed by the author (KD), across all studies contained within this thesis the outcome assessor (KD) could not be blinded to the allocated treatment arm. Participants were randomised in Study I, but study groups in subsequent studies were determined by group randomisation for the NeuroExercise study.

Finally, given that that study was dependent on numbers recruited to NeuroExercise is likely that studies II-V were underpowered on the primary outcome (BDNF) and is possible that the small sample size contributed to the null effect on study outcomes. Nonetheless, the sample size is comparable to the majority of other studies which have conducted exercise intervention studies within this cohort (Nascimento et al., 2014b, Baker et al., 2010c). Future studies with larger sample sizes are necessary to corroborate the current findings regarding BDNF upregulation.

9.14 Future Directions

Emerging evidence, targeting a variety of lifestyle factors simultaneously, have reported beneficial effects on aspects of cognition and functional abilities among at-risk older adults. The widely publicised FINGER study, a multi-domain intervention focused on diet, exercise, cognitive training and vascular risk monitoring resulted in improved cognitive performance in the intervention group compared to a control group (Kivipelto et al., 2014). Based on the FINGER intervention model, several lifestyle-based multi-domain trials are underway in a number of countries under the banner of the World Wide FINGERS interdisciplinary network (http://wwfingers.com). Given the intensive nature and time resource of the total intervention (Kivipelto et al., 2013), it will be interesting to observe whether results of the initial study are replicated. This may provide the further evidence necessary to drive policy change and implementation of this type of preventative intervention.

While not traditionally studied in exercise paradigms, research has demonstrated multicomponent type exercise interventions, with the addition of dual-task (physical exercise and cognitive intervention) or cognitive training (Ball et al., 2002) enhances cognitive function to a larger extant than traditional type exercise models (Levin et al., 2017, Muiños and Ballesteros, 2015). Improvements in cognitive outcomes have been demonstrated in older adults (Eggenberger et al., 2015, Bherer, 2015) and across a number of clinic populations including stroke (Park and Lee, 2018), Parkinson's disease (Fritz et al., 2015) and MCI (Anderson-Hanley et al., 2018, Shimada et al., 2018) following dual-task interventions. Given the enhance benefit of multicomponent type exercise, discussed previously in this chapter, future research combining exercise with cognitive training needs to be undertaken to establish if these combined interventions produce measurable cognitive change as results of the present study did not produced measurable cognitive change with exercise alone.

9.15 Summary

Regular exercise is beneficial for multiple organ systems and emerging research suggests that exercise may play a role in enhancing the BDNF profile and/or prevent or delay cognitive decline in MCI populations. Results in this thesis demonstrated that acute (high intensity exercise) and chronic (6 weeks of aerobic or balance and toning) exercise upregulates peripheral BDNF immediately post exercise in an MCI group. However, upregulation of BDNF did not produce measurable cognitive change. Within all study

groups, episodic memory and global cognition did not demonstrate a decline and remained largely stable over a one year period. Much more research is needed in human studies with regard to the effect of acute and chronic exercise on BDNF before any definitive statements concerning its effects on cognition are made.

Despite a growing body of research that supports the beneficial effects of exercise and brain health, there remains a number unresolved questions in MCI populations including: 1) the appropriate dose and modality of exercise for measurable cognitive change and 2) adherence strategies to optimise exercise uptake and participation in adults with cognitive impairment. Research suggests that a combination of exercise modalities may have more wide-ranging effects on cognitive function over only a single type of exercise. There are numerous ongoing clinical trials that will attempt to address these research questions and, hopefully, provide convincing evidence that regular exercise plays an important role in the prevention of cognitive decline in MCI and beyond. However in the current research climate, available evidence largely supports the preventative, rather than the curative neuroprotective benefits conferred by regular exercise. Therefore, exercise in line with current recommendations should continue be emphasised to optimise brain health and reduce the risk of dementia across the adult lifespan.

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11 Appendices

Appendix I: The Effects of an Extensive Exercise Programme on the Progression of Mild Cognitive Impairment (MCI): Study Protocol for a Randomised Controlled Trial

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The effects of an extensive exercise programme on the progression of Mild Cognitive Impairment (MCI): study protocol for a randomised controlled trial

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Abstract

Background: Exercise interventions to prevent dementia and delay cognitive decline have gained considerable attention in recent years. Human and animal studies have demonstrated that regular physical activity targets brain function by increasing cognitive reserve. There is also evidence of structural changes caused by exercise in preventing or delaying the genesis of neurodegeneration. Although initial studies indicate enhanced cognitive performance in patients with mild cognitive impairment (MCI) following an exercise intervention, little is known about the effect of an extensive, controlled and regular exercise regimen on the neuropathology of patients with MCI. This study aims to determine the effects of an extensive exercise programme on the progression of MCI.

Methods/design: This randomised controlled clinical intervention study will take place across three European sites. Seventy-five previously sedentary patients with a clinical diagnosis of MCI will be recruited at each site. Participants will be randomised to one of three groups. One group will receive a standardised 1-year extensive aerobic exercise intervention (3 units of 45 min/week). The second group will complete stretching and toning (non-aerobic) exercise (3 units of 45 min/week) and the third group will act as the control group. Change in all outcomes will be measured at baseline (T0), after six months (T1) and after 12 months (T2). The primary outcome, cognitive performance, will be determined by a neuropsychological test battery (CogState battery, Trail Making Test and Verbal fluency). Secondary outcomes include Montreal Cognitive Assessment (MoCA), cardiovascular fitness, physical activity, structural changes of the brain, quality of life measures and measures of frailty. Furthermore, outcome variables will be related to genetic variations on genes related to neurogenesis and epigenetic changes in these genes caused by the exercise intervention programme.

Discussion: The results will add new insights into the prevailing notion that exercise may slow the rate of cognitive decline in MCI.

Trial registration: ClinicalTrials.gov NCT02913053

Keywords: Mild cognitive impairment, Exercise intervention, Physical activity, Cognitive function, Brain structure, Frailty, Epigenetics

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Background

With an advancing aging population and associated rise in dementia prevalence in developed countries, the associated costs and disease burden have exerted significant pressure on economic and social systems [1]. To help ensure an aging society live enjoyable and productive lives, research into treating or preventing conditions such as Alzheimer's disease (AD) and other forms of age-related neurodegenerative diseases is an urgent public health priority. Today, longevity-related prevalence of neurodegenerative diseases and especially dementia, along with the current absence of a cure are among the top prominent societal health-related challenges acknowledged by the first G8 Summit on dementia held in London on December 11th, 2013 [2].

Published diagnostic criteria for AD in Lancet Neurology diagnose Mild Cognitive Impairment (MCI) as the preclinical or prodromal stage of AD [3]. In MCI, several of the clinical and neuropsychologic pathologic features are present prior to the onset of overt AD [4]. Patients with MCI in the earliest stage of neurodegeneration can be clinically diagnosed, and represent a patient cohort consistently able to participate in a structured exercise programme. Consequently, there has been an increased research focus on both pharmacological and non-pharmacological strategies to optimise cognitive function and enhance 'brain health' in older age [5], particularly for individuals at risk of developing AD [6].

Previous cross-sectional studies have established that moderate activity during midlife is associated with a lower risk of having MCI in later life, with late-life participation in moderate exercise also associated with lower risk for MCI [7]. A meta-analysis of randomised controlled trials (RCTs) by Heyn et al. [8] reported beneficial effects of physical activity on physical fitness and cognitive function in adults with cognitive impairment. In recent years, a broad range of exercise intervention studies have demonstrated cognitive benefits can be achieved with varying exercise modalities in populations with MCI [9–11]. Aerobic exercise has demonstrated significant improvements in global cognitive scores with a weak but significant effect on memory [12]. A meta-analysis by Gates et al. [13] examining the effects of chronic exercise training on cognitive function in older adults with MCI found research quality was modest, with many studies under-powered and only 8% of cognitive outcomes demonstrating statistically significant change. A limitation across a number of these studies is the small sample size and variation in MCI diagnostic criteria applied. The differing exercise approaches used across exercise intervention studies, coupled with the wide variation in cognitive tasks utilised make it difficult to summarise and synthesise research findings [14].

There is converging evidence from animal and human studies that regular aerobic exercise acts as a promoter of 'brain health' mediating neural homeostasis and, via neuroprotective and neurorestorative mechanisms, thereby counteracting brain ageing. At the behavioural level, exercise has been found to upregulate affective states [15, 16] and to improve cognition throughout different age phases [17–19] and different dimensions, including spatial/associative learning [20, 21], attentional processing [22], and executive control [23]. While animal research has allowed the unravelling of the underlying neurobiological mechanisms of exercise at the behavioural (e.g. water maze-type tests), cellular (e.g. neurogenesis, synaptogenesis, neuroangiogenesis), and humoral (e.g. neurotrophic factors, inflammatory cytokines) levels [24, 25], so far the neurobiological and epigenetic effects of exercise remains poorly understood in humans. While preliminary results indicate that aerobic exercise inhibits the progression of AD-like neuropathology in an animal model [26, 27], currently there is little information about the effects of regular physical exercise on the progression of both functional and structural markers at the pre-dementia and early dementia stages in humans.

The aim of this study is to compare a 12-month structured exercise programme (aerobic and stretching and toning group) to a control group for progression of cognitive decline in MCI. The stretching and toning group will act as a non-aerobic exercise group, controlling for the social effect of a structured group exercise programme. This type of low-intensity exercise intervention has previously shown some positive effects on cognitive outcomes, as it provides participants with equivalent opportunity for social interaction [28]. Previous exercise intervention studies in MCI that have utilised non-aerobic exercise (e.g. stretching and toning) as a control intervention have noted some improvement in cognitive performance [8, 29] while others have not demonstrated significant change in cognitive performance [9, 10]. The comparison between aerobic exercise, non-aerobic exercise and a control group coupled with the 12-month intervention period, concomitant brain scanning, genetic and epigenetic analyses is innovative and will be a strong addition to the growing body of literature around exercise in MCI.

Methods/design

Study aims

The primary aim of this study is to investigate the effects a 12-month structured exercise programme (aerobic, and stretching and toning group) compared to a control group for the progression of cognitive decline in MCI. The primary hypothesis of this study is that participation in an extensive exercise programme will demonstrate a slower rate of cognitive decline compared to the control

group. A secondary hypothesis is that participants in the aerobic exercise group will demonstrate a stronger positive effect of cognitive functioning than the stretching and toning (non-aerobic) group.

The secondary aims of this study are:

1. To examine the effects of a structured exercise programme on MoCA scores, a screening tool of global cognition in MCI
2. To determine the effects of a structured exercise programme on cardiovascular fitness
3. To measure the effects of a structured exercise programme on physical activity levels
4. To investigate a mechanism of action through epigenetic analysis and exploration of structural and functional changes on Magnetic Resonance Imaging (MRI) brain pre and post 12-month intervention
5. To investigate the effects of a structured exercise programme on quality of life measures and measures of frailty

Study design

This proof of concept will take the form of a randomised controlled trial to be completed across three centres in Europe; the German Sport University Cologne, Germany, University of Nijmegen, The Netherlands and Trinity College Dublin, Ireland. A total of 225 participants will be randomised ($n = 75$ at each site) to either a yearlong supervised and home based aerobic exercise programme ($n = 75$), an equivalent non-aerobic stretching/toning programme ($n = 75$) or to the control group ($n = 75$). The primary outcome will be change in cognitive performance as measured by a neuropsychological test battery. Secondary outcomes will include changes in MoCA scores, cardiovascular fitness, physical activity, quality of life measures, measures of frailty, epigenetic and structural changes. Change in all outcomes will be measured at baseline (T0), after six months (T1) and after 12 months (T2) (see Fig. 1).

Recruitment and screening

In total, 225 previously sedentary adults aged 50 years or older who are diagnosed with MCI will be recruited via hospital memory clinics affiliated with the three sites and from the community. Advertising will take place through community centres and newspaper articles. Initial screening will be completed over the telephone to determine eligibility. Participants who meet the following diagnostic, inclusion and exclusion criteria and successfully complete baseline measures including a screening exercise test will be enrolled.

Diagnostic criteria

Participants will have a diagnosis of MCI due to AD according to the Albert et al. [3] criteria. All enrolled participants with MCI will be classified as having memory decline but not dementia (Clinical Dementia Rating global score = 0.5), consistent with established MCI classification [3, 30].

Inclusion criteria

Participants who meet the following criteria will be eligible to participate: (1) MoCA [31] 18–26; (2) stable medical condition for more than 6 months; (3) stable medication for more than 3 months; (4) adequate visual and auditory acuity to complete neuropsychological testing; (5) electrocardiogram without significant abnormalities that might

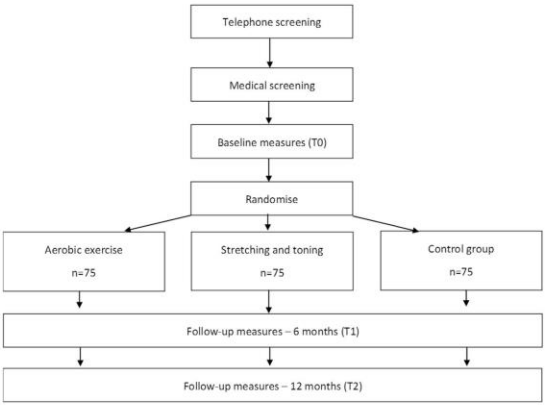

Fig. 1 Participant flow through study

interfere with the study; (6) physical ability sufficient to allow performance of endurance exercise training; (7) capacity to provide written and dated informed consent form; (8) medical clearance to undergo a symptom-limited cardiopulmonary exercise test and extensive aerobic exercise training.

Participants recruited from the community via newspaper articles and community advertisement will complete additional testing to determine MCI status. To distinguish between amnestic and non-amnestic MCI, agreed education adjusted cut-offs of -2 Standard Deviation (SD) for low education (<10 years of education), -1.5 SD for the middle group (10–13 years of education) and -1 SD for the highly educated (>13 years of education) will be taken from the delayed recall portion of an age adjusted episodic memory test. In Nijmegen and Dublin this will be evaluated using the Logical Memory (story recall) subtest of the Wechsler Memory Scale (WMS-IV) [32, 33]. In Cologne, education scores will be examined using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) [34] Delayed Memory Index (Score of < 85).

Exclusion criteria

Participants will be deemed ineligible if they meet any of the following criteria: (1) diagnosis of AD or other type of dementia; (2) history of familial early-onset dementia; (3) enrollment in any investigational drug study; (4) history in the past 2 years of epileptic seizures (participants with epilepsy who have been stable off medication or seizure free for 2 years may be included); (5) any major psychiatric disorder (a clinical diagnosis of major depressive disorder, bipolar or schizophrenia); (6) past history or MRI evidence of brain damage, including significant trauma, stroke, hydrocephalus, mental retardation, or serious neurological disorder; (7) carotid stent or severe stenosis; (8) history of myocardial infarction within previous year; (9) congestive heart failure (New York Heart Association Class II, III or IV) (10) uncontrolled hypertension or hypotension (systolic blood pressure >200 mm Hg and/or diastolic blood pressure >110 mm Hg at rest) [35]; (11) unstable cardiac, renal, lung, liver, or other severe chronic disease; (12) type 2 diabetes mellitus with hypoglycemia in the last 3 months; (13) significant history of alcoholism or drug abuse within last 10 years; (14) engagement in moderate-intensity aerobic exercise training for more than 30 min, 3 times per week, during past 2 years; (15) history of vitamin B12 deficiency or hypothyroidism (stable treatment for at least 3 months is allowed); (16) serious or non-healing wound, ulcer, or bone fracture

In Cologne and Nijmegen, participants will be invited to complete brain MRI scans. Participants with pacemakers or other medical metal devices will not be eligible for MRI scanning as per standard procedures.

Withdrawal of participants

The investigator can decide to withdraw a subject from the study for urgent medical reasons. Subjects can leave the study at any time for any reason if they wish to do so without any consequences. All primary analyses will be performed on an intention-to-treat basis with all randomised participants included in the primary analyses. Participants who withdraw from the study will be invited to attend T1 and T2 assessments.

Randomisation, allocation, concealment and blinding

Following baseline assessment, participants will be randomised to one of three arms using a centrally controlled computer generated randomisation list (for each country) generated by an independent statistician. Participants will be randomised to one of three arms as per Fig. 1. At each centre, the investigators will be blinded to allocation order and the treatment will be assigned using sealed envelopes based on order of recruitment. Outcome assessors and exercise trainers will not be blinded to the allocated treatment arm.

Interventions

Exercise intervention

The aim of both the aerobic intervention and stretching and toning exercise intervention groups will be to accrue 3 x 45 min exercise sessions per week over 12 months. Participants will complete a combination of supervised instructor led classes and unsupervised home exercise sessions. Class attendance and adherence to unsupervised home exercise sessions will be recorded for each participant by the class instructor each week over the 12 month intervention period.

The goal of the aerobic exercise class will be to accumulate at least 45 min of extensive aerobic exercise, prescribed by heart rate (HR) calculated as 180 bpm – age. Exercise intensity will be monitored during the supervised classes using a HR monitor and subjective reporting of the exercise intensity using the Borg's Rating of Perceived Exertion (RPE) [36]. Participants in the aerobic exercise group will aim to achieve a target RPE of 13 while exercising. Each supervised class will be comprised of a 5–10 min warm up, 45 min of targeted aerobic exercise and a 5–10 min cool down. A range of aerobic exercise modalities will be offered including cycling, treadmill walking, elliptical training, endurance related indoor activities, outdoor walking, jogging and aqua jogging.

The aim of the stretching and toning group will be to complete non-aerobic activities. Each supervised class will be comprised of a 5–10 min warm up, 45 min of stretching, balance, coordination, relaxation, group games and light resistance exercises and a 5–10 min cool down. During the stretching and toning class,

exercise intensity will not exceed an RPE of 10. Participants in the stretching and toning group will not be advised about aerobic activity and will not be instructed to avoid completing routine aerobic activity. The stretching and toning group will act as a social control group and it is not anticipated to see significant improvement in study outcomes.

The control group will receive usual care and will not be advised about exercise or attend supervised sessions. Participants in the control group will complete outcome assessments.

Outcome assessment

All outcomes will be measured at T0 (Baseline), T1 (6 months) and T2 (12 months) time points. Brain MRI, blood sampling for epigenetic analysis and the NEO-Five Factor Inventory (NEO-FFI) will only be measured at T0 and T2. All participants will undergo described tests, except for MRI (only in Cologne and Nijmegen).

Primary outcome

Cognitive function

The primary outcome is cognitive performance. Cognitive performance will be assessed by a neuropsychological test battery measuring six cognitive domains. The test battery will consist of a computer based CogState Battery including the International Shopping List Task (ISLT) – immediate and delayed recall, Detection Task, Identification Task, One Back Task and One Card Learning Task (https://cogstate.com/) [37, 38], Verbal fluency [39, 40] and Trail Making Test (TMT) [41].

The allocation of to the tests to the six cognitive domains is based on the CogState Guidelines and conventional classification of neuropsychological tests [42]. *Verbal memory* will be assessed by ISLT. *Psychomotor function* will be measured with the Detection Task. *Executive function* will include TMT-B, Letter Fluency and Category Fluency. *Attention* will be assessed by the Identification Task and TMT-A. *Working memory* will be measured by One Back Task, and *Visual memory* by the One Card Learning Task. A description of the tasks is described below.

The CogState battery will take approximately 30 min to complete. The ISLT is a 12 word, four trial (three learning trials and one delayed recall trial). Total number of correct responses made in remembering the list on three consecutive trials at a single session and after a delay will be recorded. The ISLT has been shown to have good sensitivity to verbal memory impairment [43]. The Detection Task measures psychomotor functioning and speed of processing. Participants must respond as quickly as possible when the card shown face down in the centre of the screen flips over by pressing a button on the keyboard. Reaction time is measured with lower scores indicating better performance. The Identification Task measures visual attention. Participants must decide whether a playing card presented on screen is red, by pressing the 'Yes' or 'No' button. Reaction time is measured and lower scores indicate better performance. The One Back Task assesses working memory. Participants are presented with a sequence of playing cards in the centre of a screen and must decide if the card presented is the same as the one shown immediately before. The One Card Learning Task measures visual learning and memory. Participants are presented with a succession of playing card on screen, and must decide if the card currently displayed has been displayed previously. Accuracy of performance is measured, with higher scores indicating better performance. A number of studies have found that the CogState battery of tests are sensitive to detecting cognitive impairment in mild to moderate AD and amnestic MCI populations relative to healthy matched controls [44]. CogState and has been validated across a broad range of cognitively impaired populations [38].

Verbal fluency will be assessed with Letter Fluency [39] and Category Fluency [40]. For the Letter Fluency test participants are allowed one minute to generate as many words as possible that begin with a specific letter. This task will be repeated three times with three different letters (e.g. F, A, S). For the category fluency test, participants must give as many examples of animals as possible within one minute.

TMT will be completed as a paper and pen based task. The TMT consists of two sub trials. TMT-A require individuals to sequentially connect 25 encircled numbers on a sheet of paper, while TMT-B require participants to draw a line, alternating between numbers and letters in ascending order.

Secondary outcomes

Secondary outcomes will include global cognitive function, cardiovascular fitness, physical activity, quality of life, depression, measures of frailty and epigenetic changes.

MoCA screening tool will be used as a broad measure of global cognitive function. The MoCA is a one-page 30-point test administered in 10 min which consists of 13 tasks covering the following eight cognitive domains: visuospatial/executive functions, naming, verbal memory registration and learning, attention, abstraction, delayed verbal memory, and orientation. It has demonstrated high sensitivity and specificity as a cognitive screening instrument and has been validated to detect MCI [31].

Cardiovascular fitness will be assessed using an incremental exercise test on a standard cycle ergometer. Participants at the German Sports University and Trinity College Dublin will complete a maximal test in accordance with the World Health Organisation Protocol [45]. The test will commence with 3 min cycling unloaded, followed by the incremental phase of exercise during which the load will increase by 25 W every two minutes

until the test is terminated. Blood lactate levels and participants reported BORG RPE scores will be measured at each stage of the test (2 min intervals). At the University of Nijmegen, aerobic fitness will be estimated from a submaximal exercise test completed according to the Astrand-Rhyming submaximal protocol [46]. During the first two minutes, resistance of the ergometer will be increased until a steady state HR of 70% of the estimated maximal HR is reached. Participants continue pedalling for 6 min. HR and RPE will be recorded every minute. VO_2max will be estimated using the average HR of minute 5 and 6 and the work load in the Astrand Nomogram.

Physical activity will be assessed objectively using an activity accelerometer to be worn for seven consecutive days by study participants as each assessment time point and subjectively with the LASA Physical Activity Questionnaire (LAPAQ). The LAPAQ questionnaire is a valid and reliable self-reported questionnaire that captures physical activity over the preceding 14 days [47].

Health related quality of life will be evaluated using the Health Related Quality of Life for People with Dementia (DemQOL). DemQOL is a 28 item interview administered questionnaire relating to different aspect of QOL. The DemQOL has been validated in a large sample of people with dementia and demonstrates good acceptability and internal consistency [48]. It has also been used in older adults and in patients with MCI [49]. In addition, the Center for Epidemiologic Studies Depression (CES-D) questionnaire will be administered to determine depressive symptoms. The CES-D Scale is a short self-report questionnaire that measures symptomatic depression [50] that has been validated as a depression screening tool in older adults [51]. Depressive symptoms are associated with increased risk of MCI [52]. The association of depression with prevalent MCI and with progression from MCI to dementia, but not with incident MCI, suggests that while depression is prevalent in MCI, it does not precede it [53].

Measures of frailty will include The Timed Up and Go (TUG) test, hand grip strength and 30 s chair stand. The TUG will assess the participant's mobility and balance. The TUG is a reliable and valid test for quantifying functional mobility and is useful in following clinical change in frailty over time [54]. Hand grip strength will be measured using a Jamer Digital Dynamometer as a measure of upper limb strength. A standardised approach will be taken to obtaining the measurement [55]. Hand-Grip strength has been shown to predict future outcomes in aging adults including mortality and future levels of disability [56]. The 30 s chair stand will determine lower limb strength and endurance. Lower body strength is considered critical in evaluating the functional performance of older adults [57].

Venous blood samples will be collected for genetic and epigenetics analysis performed on a Sequenom Massarray Analyzer 4 at the Department of Psychology University of Bonn, Germany. Genotyping of the Apolipoprotein E (APOE) and the Brain Derived Neurotrophic Factor (BDNF) genes and their epigenetic methylation patterns will be the primary focus. The genetic analyses will serve as predisposed risk and resilience factors for cognitive functioning and decline in MCI participants. The epigenetic findings will shed new light on the link between exercise and gene activation of relevant genes in the biochemical pathways underlying cognitive decline. Given the moderating effect of the common genetic variation of APOE via personality on AD onset [58], the NEO-Five Factor Inventory (NEO-FFI) will be included to assess personality traits such as neuroticism or extraversion, predicting an earlier onset of Alzheimer and cognitive decline in elderly humans [59]. NEO-FFI is a psychological personality inventory consisting of 60 items to measure five personality traits. The questionnaire will be completed following each blood draw to form part of the epigenetics analysis. The NEO-FFI is also discussed as a measure of emotional intelligence [60].

Structure and function of related brain regions will be measured using functional MRI (fMRI) brain which is a non-invasive method for examining brain activity and structure. Structural imaging will include isotropic T1-weighted-, T2-weighted- and FLAIR- sequences with an isotropic spatial resolution of 1x1x1mm. The combination of the different image weightings allows for an automatic detection/volumetry of white matter lesions. Additionally, the combination of these sequences improves image segmentation. The structural protocol will be rounded up by a 3D-DTI sequence (60 diffusion directions, 1.7x1.7x1.7 mm) and a resting state fMRI Table 1.

Safety

All serious adverse events (SAE)/adverse events (AE) will be recorded on study specific adverse event forms. All AE's will be registered with the local principle investigator (PI). These will be discussed at regular team meetings and collected and registered at the end of the study. All SAE's will be registered centrally. In the case of an SAE, all site PI's will be informed both at time of occurrence (with 24 h) and for a final conclusion on causality.

Sample size

The sample size estimation was performed in "G*Power", a statistical software program. The effect size was estimated, based on the effect size found in several studies examining the effect of exercise on cognition in elderly with MCI or increased risk for AD [8–10, 61, 62]. Sample size was

Table 1 SPIRIT diagram outlining schedule of enrolment, interventions, and assessments for study participants

Timepoints		Pre-screening telephone call	Baseline assessment T0	Study assessment T1	Study assessment T2
			<13 days following screening	6 months after study visit 1	12 months after study visit 1
Enrolment	Explain study	X			
	Screen eligibility criteria	X			
Study Outcomes	Neuropsychological testing		X	X	X
	MoCA		X	X	X
	DemQOL		X	X	X
	CES-D		X	X	X
	Incremental Exercise Test		X	X	X
	Physical Activity Tracker		X	X	X
	LAPAQ		X	X	X
	Blood sampling		X		X
	NEO-FFI		X		X
	MRI Brain[a]		X		X
	TUG		X	X	X
	Hand Grip Strength		X	X	X
	30 second chair stand		X	X	X
	Randomisation (after completion of all baseline assessments)		X		
	Exercise intervention[b]		X	X	X

[a]MRI brain will be performed in Cologne and Nijmegen sites
[b]After completion of T0 assessment, participants will be randomised to one of the three groups (aerobic exercise, stretching and toning exercise, control group). Exercise intervention will be continuous for a 12-month duration following completion of T0 assessments

calculated based on a two-tail statistical t-test set 1-β = 0.80, α = 0.05, an effect size of 0.4, an allocation ratio N2/N1 of 2. A total sample size of 224 was calculated. Considering a correlation of 0.5 between the outcome measures at T0 and T2, the design design-factor D = 1-0.52 = 0.75. The expected dropout rate is 25%. 224*0.75*1.25 = 210. Considering the fact that the primary analysis will be a combination of the results of three different centres, the final sample size $n = 210$ is rounded up to $n = 225$.

Statistical analysis

The primary analysis of this study will be comparison of cognitive functioning (primary outcome measure) between all three intervention arms before (T0) and after (T2) the 1 year intervention. A composite score will be calculated by averaging all six domain scores into one overall cognition score. The obtained scores per test will be converted into z-scores based on the standard deviation and mean of the total sample at baseline. In case of multiple tests within one domain, the average z-score for the domain will be calculated. Secondary outcome measures are the six separate cognitive domain scores and the other parameters.

For the primary analysis we will have an intervention group of $n = 150$ (both exercise forms together) and a control group of $n = 75$ as input of an ANCOVA with dependent variable the change in cognitive composite score between T2 and T0, and as covariates baseline cognitive functioning, sex, age. In a secondary analysis the comparison between the two exercise forms will be carried out in a similar ANCOVA analysis.

Analyses for all secondary outcome parameters will be carried out with similar ANCOVA analyses. Secondary analyses will also elucidate the contrasts between T0 and T1 and T2 for the primary and secondary outcomes, and thus elucidate the course over time, without correction for multiple comparisons, as these analyses are exploratory.

Furthermore, to assess change in physical fitness, quality of life, cerebral structure and epigenetics a similar statistical approach will be used as for the primary study parameter. A p-value of < 0.05 will be used to assess statistical significance.

Data management

All data will be managed using unique study codes to protect participant confidentiality, which will be used to code and file all electronic information. The key linking this code to participant identity will be stored in a secured file, access to this key is available only to designated members of the research team at each site. Raw data

will be stored in a file cabinet with a lock where only designated research team members will have access to the key.

Discussion

To the best of our knowledge, there have been no intervention trials evaluating the effect of an extensive, controlled and structured 12-month exercise programme on the progression of cognitive decline in an MCI population. Since the neuropathological change process can take years after onset of MCI, the addition of longer intervention period may result in larger intervention effects. An important consideration of this study is the isolated aerobic exercise intervention. A number of exercise intervention studies have implemented multimodal exercise interventions [11, 63], making it difficult to interpret the effect of isolated exercise modalities. The large sample size, longer duration of exercise intervention, comprehensive neuropsychological test battery will enhance the existing research around exercise and cognitive function in MCI.

The secondary outcomes will examine several potential underlying mechanisms that may influence the exercise-cognitive relationship in MCI. The effect of exercise on brain structure and function measured by MRI brain will be examined. Methylation analyses of the APOE gene and neurotrophic genes will explore the effects of exercise on this known AD risk factor. Static gene polymorphisms will be used to predict intervention outcomes. Finally, cardiovascular fitness will be measured and examined as a moderator of the exercise-cognitive relationship in MCI. While cognitive performance is the primary outcome, we will also assess whether participation in a structured exercise programme or changes in cognition can influence quality of life and measures of frailty, known risk factors for cognitive further decline [64].

Abbreviations

AD: Alzheimer's disease; AE: Adverse event; ANCOVA: Analysis of covariance; APOE: Apolipoprotein E; BDNF: Brain derived neurotrophic factor; CES-D: Center for epidemiologic studies depression; DemQOL: Health related quality of life for people with dementia; fMRI: functional magnetic resonance imaging; HR: Heart rate; ISLT: International shopping list task; LAPAQ: LASA physical activity questionnaire; MCI: Mild cognitive impairment; MRI: Magnetic resonance imaging; NEO-FFI: NEO-five factor inventory; RBANS: Repeatable battery for the assessment of neuropsychological status; RCT: Randomised controlled trial; RPE: Rate of perceived exertion; SAE: Serious adverse event; SD: Standard deviation; TMT: Trail making test; TUG: Timed up and go; WMS: Wechsler memory scale

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Availability of data and materials

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

Authors' contributions

SS, BL and MOR developed the idea for the study. KD, EG and MS drafted the protocol with input from all authors on study design and revisions to the protocol paper. All authors have approved the final version of this paper prior to submission.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethics approval and consent to participate

The study protocol is approved by the Tallaght Hospital/St. James's Hospital Joint Research Ethics Committee Dublin Ireland (reference 2015/09/04; 14/12/2015), the German Sport University, Cologne Germany (reference 9/2015; 21/01/15) by Commissie Mensgebonden Onderzoek Arnhem-Nijmegen, Netherlands (reference 2015-1872).

Publisher's Note

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Appendix II: Real World Recruiting of Older Subjects with Mild Cognitive Impairment for Exercise Trials: Community Readiness is Pivotal

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Short Communication

Real World Recruiting of Older Subjects with Mild Cognitive Impairment for Exercise Trials: Community Readiness is Pivotal

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Abstract. Prevention trials in subjects with mild cognitive impairment (MCI), especially lifestyle interventions, can be difficult to carry out, particularly the recruitment and retention of subjects. We experienced these challenges in our multi-site one-year exercise trial in MCI, NeuroExercise. Trial recruitment rates differed significantly across sites; the non-medical sport university site, providing free access to a range of group exercise in a sports environment, proved far more successful than memory clinics linked to hospitals. This suggests that non-medical settings and a non-medical research community facilitating physical activities may be important factors in recruitment of subjects with MCI for large prevention trials.

Keywords: Attrition, exercise, mild cognitive impairment, prevention, recruitment, selection

INTRODUCTION

As the need for high quality intervention trials to prevent dementia at preclinical and pre-symptomatic stages grows, effective and efficient recruitment and selection strategies are required for intervention trials targeting disease modification and primary prevention [1, 2]. Recruitment can be particularly difficult and expensive to achieve in older subjects with cognitive decline, who rely to a large extent on their caregivers' willingness and availability to support them [3, 4]. In our multicenter NeuroExercise prevention trial in mild cognitive impairment (MCI), we encountered differences in recruitment rates between sites, which we decided to study in more detail to

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see if there were site specific factors that might guide recruitment strategies for prevention trials going forward. The Neuroexercise trial is registered at ClinicalTrials.gov as: NCT02913053.

MATERIALS AND METHODS

The NeuroExercise project is a randomized controlled clinical intervention study, carried out across three European sites: the Sport University Cologne (Germany), the academic department of old age psychiatry in Dublin (Ireland), and the academic geriatric department in Nijmegen (The Netherlands). Details on the study methods were published in the design paper; here we limit ourselves to the essentials [5]. For the intervention and control group, seventy-five previously sedentary patients, aged 50 or over, with a neuropsychologically defined diagnosis of MCI according to the criteria of Albert et al. [6], had to be recruited per site. These were randomized to one of three groups: a standardized 1-year extensive aerobic exercise intervention (3 visits of 45 min/week), a group with a stretching and toning (non-aerobic) exercise program (3 visits of 45 min/week), and a control group without exercise intervention. Cognitive, physical fitness, and epigenetic outcome measurements are carried out at baseline, after six and 12 months. For further details on inclusion and exclusion criteria, we refer to the trial protocol [5]. To facilitate recruitment, we chose to recruit subjects from memory clinics (MC) of the linked Alzheimer centers, from the community via advertisements in local newspapers and via other channels, that did not differ significantly across sites. In Nijmegen, subjects were also recruited subjects via a network of active aging interventions in the community. In Dublin, subjects were also recruited via other public communications (advertisements in GP practices, radio interviews). In Cologne, modern social media was also used to recruit subjects. The subjects recruited were those subjects who responded to the advertisements and the information obtained at the memory clinic. All subjects recruited were preliminary assessed for eligibility via telephone interview. If meeting the inclusion criteria that could be checked by telephone, they were invited for the further screening procedure, at which it was confirmed whether they met inclusion or exclusion criteria and if it was safe to participate in the one year exercise intervention [5]. The recruitment and selection procedures were similar across sites and approved by the three local ethics committees. Differences in descriptive variables and in recruitment ratios were tested via ANOVA (for continuous variables) and Chi-square tests (category variables).

RESULTS

Over the 18-month recruitment phase, recruitment rate via the memory clinics was low but did not differ across sites (See Table 1). However, the community based inclusion ratios were on average 283% for the included/recruited ratio (17% versus average of 5% and 7%) and 294% for the included/screened (50% versus average of 19% and 15%) higher at the German Sport University than the average of the equivalent ratios at the other sites ($p = 0.0001$). Moreover, the period needed for recruitment was much

Table 1
Comparison of recruitment and inclusion of older subjects with mild cognitive impairment between sports university (Cologne), and university medical centers (Dublin, Nijmegen) for an exercise intervention

Setting	Cologne		Dublin		Nijmegen		*p*
	MC	C	MC	C	MC	C	
Recruited N	63	350	157	534	48	376	P1-MC: 0.331
Screened N	28	115	43	134	16	174	P2-MC: 0.588
Included	20	58	35	25	12	27	P1-C: 0.0001*
N (%1; %2)	(32;71)	(17;50)	(22;81)	(5;19)	(25;75)	(7;15)	P2-C: 0.0001*
Age: y (SD)	73.1 (5.5)		70.9 (1.4)		69.6 (8.3)		0.001**
Sex: % female	46		55		33		0.110
Education y (SD)	13.3 (2.3)		12.9 (4.9)		13.6 (4.0)		0.645
MOCA	22.8 (0.7)		21.9 (0.7)		22.8 (2.5)		0.001**

MC, memory clinic; C, community; MOCA, Montreal Cognitive Assessment (0–30, highest score: best); SD, standard deviation; *differences between the average of the medical centers and the sport university; **ANOVA of between group age differences in age, education, and MOCA. %1, percentage of subjects included versus subjects recruited; %2, percentage of subjects included versus subjects screened; P1, percentage of subjects included versus subjects recruited; P2, percentage of subjects included versus subjects screened; P1-MC/P2-MC, Chi-square test on differences in P1/P2 between MCs; P1-C/P2-C, Chi-square tests on differences between sport university and average of MCs in P1/P2.

lower (<2 weeks) in Cologne, versus 18 months in Dublin and Nijmegen. Age and Montreal Cognitive Assessment scores of the subjects included in Cologne were higher ($p = 0.001$). Regarding barriers and facilitating factors to participate, the subjects in Cologne indicated that the sports facilities and the non-medical, positive atmosphere in the group sessions at the German Sport University encouraged participation. The barriers to participation mentioned by all groups were the long duration of the intervention, lack of interest, the difficulties in transportation to and from the intervention site, and the burden this resulted in for partners or other accompanying relatives.

DISCUSSION

In this multi-center NeuroExercise trial, in which we aimed to test a one year exercise intervention in MCI, subject recruitment overall was challenging. Offering the same intervention at a non-medical site, using similar advertisements, where there was no experience in MCI or dementia trials, was much more successful than recruitment through the memory clinics/Alzheimer centers. This site-specific difference in recruitment rate has not been previously described [7, 8].

One important factor was the ready availability of an existing exercise and sports facility within the Cologne community, which could be freely accessed by the German participants. We hypothesize that the more health oriented, non-stigmatizing community setting of the German Sport University also lowered the threshold for subjects with an MCI diagnosis or those experiencing memory complaints and not having a formal MCI diagnosis to get in contact with the research team. Future trials on exercise in MCI should consider recruiting from a community population, and try and ensure that the community environment is ready to facilitate the intervention so that it is attractive and easy for the subjects to participate. This community readiness approach for exercise intervention trials would require collaboration between medical and non-medical academic departments, community agencies, and older subjects. Our findings also show that the field could benefit from an evidence-based guideline on cost-effective research methods for recruitment and other trial methodologies for the conduct of high quality prevention interventions in subjects with cognitive decline [9, 10].

ACKNOWLEDGMENTS

The Neuro-exercise studies are supported by The EU Joint Programme – Neurodegenerative Disease Research (JPND). German grant number BMBF 01ED1510A. Health Research Board Ireland grant number JPND-2014-1. Dutch grant number: ZonMw 733051044.

Authors' disclosures available online (https://www.j-alz.com/manuscript-disclosures/17-1083).

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Appendix III: Exercise and Alzheimer's disease: Current Perspectives

Exercise and Alzheimer's disease: current perspectives

There is growing evidence that exercise may boost cognition and reduce neuropsychiatric symptoms, even in symptomatic Alzheimer's disease, write

Kate Devenney, **Dr Emer M Guinan** and **Prof Brian Lawlor**

AS THE POPULATION ages, the number of people in Ireland living with dementia is projected to rise from an estimated 55,000 in 2016, to 77,000 by 2026.[1] To help ensure our ageing society lives productive lives, research into treating, preventing and managing conditions such as Alzheimer's disease and other forms of age-related neurodegenerative diseases is an urgent public health priority.

Today, the longevity-related prevalence of neurodegenerative diseases, especially dementia, and the current absence of a cure are among the top prominent societal health-related challenges.[2] Current pharmacological treatment for Alzheimer's disease is symptomatic and can only temporarily stabilise the illness. New, potential disease-modifying treatment strategies have not yet demonstrated clinically relevant effects, highlighting the need for continued research into non-pharmacological treatments and interventions that address modifiable risk factors.[3]

Exercise and its role in dementia prevention is at the forefront of the research agenda in Alzheimer's disease. An emerging area of research is now examining whether physical exercise can slow the progression or improve symptoms in people with prodromal or symptomatic Alzheimer's disease. This review will examine the evidence for exercise interventions in people with mild cognitive impairment and Alzheimer's disease.

Physical activity in healthy older adults

In recent years, convincing evidence has shown that regular physical activity can reduce the risk of cognitive decline, AD and other dementias.[4,5] A systematic meta-analysis of prospective studies examined the association between physical activity levels and risk of cognitive decline in healthy subjects (33,816 non-demented subjects) and found high levels of physical activity reduced the risk of future cognitive decline by 38% (hazard ratio (HR) 0.62, 95% confidence interval (CI) 0.54–0.70; $P < 0.00001$).[6] Analysis of low and moderate physical activity also showed significant protection (reduced risk 35%) against cognitive impairment (HR 0.65, 95% CI 0.57–0.75; $P < 0.00001$).

In older adults identified at risk of cognitive decline, moderate physical exercise was shown to improve cognitive function.[7] The Irish Longitudinal Study on Ageing (TILDA) examined physical activity levels in 8,172 adults aged 50 years and older and found two-thirds of this population reported low or moderate levels of physical activity, while only one-third reported high levels of activity.[8] It was also found that low physical activity is almost twice as prevalent in those aged 75 years and older. These findings are in agreement with the Healthy Ireland Survey which found that physical activity decreases with age, with only 15% of those aged 65 and over considered highly active.[9]

From examining the figures relating to physical activity in Ireland, it can be concluded that the majority of older Irish adults are not meeting World Health Organization international activity guidelines that recommend at least 150 minutes of moderate intensity aerobic physical activity throughout the week (performed in bouts of at least 10 minutes) and muscle strengthening activities (two or more days per week) for a 20-30% lower risk of dementia.[10,11]

Exercise and brain function

It is has long been established that exercise has a positive effect on a number of physiological functions and more recently the impact on brain health and cognitive function have been explored. There is converging evidence from both animal and human studies that regular physical exercise acts as a promoter of brain health, mediating neural homeostasis and counteracting the effects of brain ageing.[12] Potential mechanisms to account for the exercise-cognitive relationship include favourable effects on neuronal survivability and function, neuro-inflammation, vascular health, neuroendocrine response to stress, and brain amyloid burden. In healthy subjects, the beneficial effects of physical exercise is supported by studies showing increased memory performance and at the same time increased whole-brain and hippocampal volumes,[13] as well as increased activity in neural networks.[14]

Exercise in mild cognitive impairment

Mild cognitive impairment is considered an intermediate stage between the cognitive change associated with normal ageing and dementia.[15] Mild cognitive impairment may represent a clinical prodrome to Alzheimer's disease and other dementias, with 10-15% of people with mild cognitive impairment progressing to dementia per year.[16] No pharmacological interventions have been shown to slow the rate of cognitive decline in this patient population. Exercise, if implemented at the earliest possible stage of the neurodegenerative process, may alter the disease trajectory and help slow the rate of cognitive decline.[12]

The first of a number of randomised controlled trials using rigorous controlled methodology to examine the role of exercise in mild cognitive impairment was published by Baker et al in 2010.[17] Participants were randomised to a high intensity aerobic exercise or stretching

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control group. The aerobic group performed supervised exercise at 75-85% of heart rate reserve for 45-60 minutes per day, four days per week for six months. The control group carried out supervised stretching activities according to the same schedule. Findings indicated that a high intensity aerobic intervention had sex-specific effects on executive control processes for older women at high risk of cognitive decline.

Following on from this landmark study, a broad range of exercise intervention studies have demonstrated that cognitive benefit can be achieved with varying exercise modalities (primarily aerobic training and more recently resistance type training) in populations with mild cognitive impairment.[17,18,19,20] Several meta-analyses have reported that increased activity levels in those with known cognitive impairment are associated with improvements in a number of cognitive processes, including attention, processing speed and executive function.[21,22] A number of meta-analyses that examined the effects of isolated aerobic training on cognition in individuals with mild cognitive impairment found significant improvement in global cognitive scores, with one meta-analysis also reporting a weak, but significant effect on memory.[23,24]

While evidence to date indicates that exercise may be of cognitive benefit to this patient population, exactly what exercise prescription (frequency, intensity, time and type) and which particular cognitive domains are malleable to exercise intervention remains uncertain. However, when considering the evidence in its entirety, aerobic type exercise of moderate to high intensity appears to produce the greatest cognitive benefit in mild cognitive impairment although it can take a sustained period of up to six months of exercise training for cognitive benefit to become evident.[18,23,25]

Exercise in Alzheimer's disease

Until recently, little evidence existed for the role of physical exercise in people with Alzheimer's. While it is now thought that exercise or regular physical activity might play a role in both protecting the brain from Alzheimer's and other dementias, it may also have a role in helping people to live better with the disease.

Previously published exercise intervention studies in Alzheimer's disease have demonstrated inconsistent findings.[17,26,27] Many studies were performed in moderate to severe stages of the disease with the physical activity interventions being investigated often not supervised or monitored. The most recent Cochrane review[26] of physical activity for people with dementia concluded that some promising evidence suggests that exercise programmes may improve the ability to perform activities of daily living in people with dementia, but no conclusive evidence supported the benefits of exercise on cognition, neuropsychiatric symptoms or depression in dementia. Overall, the quality of studies included in the review was reported as very low, highlighting an ongoing need for further large, randomised trials of exercise in people with Alzheimer's disease and dementia.

Whether physical exercise could improve symptoms in people with Alzheimer's disease, or beneficially impact the brain changes caused by the disease, has been the focus of a number of RCTs in more recent years. At the

Table 1. Key messages

- Only one-third of Irish adults aged 50 and over report high levels of physical activity
- In cognitively normal subjects, high levels of physical activity have been shown to be significantly protective (38% reduced risk) against future cognitive decline
- Physical exercise may slow the progression of cognitive decline or improve neuropsychiatric symptoms in people with prodromal or symptomatic AD
- Guidelines suggest 150 minutes of moderate intensity aerobic physical activity per week and muscle strengthening activities for a 20-30% lower risk of dementia
- Higher activity levels in those with known cognitive impairment are associated with enhanced cognitive processes across a number of cognitive domains including attention, processing speed and executive function

2015 Alzheimer's Association International Conference, Hanseltbalch et al from the Danish Dementia Research Centre reported results from the Danish ADEX study.[28] In the ADEX study, 200 people with mild to moderate Alzheimer's disease were randomly assigned to either a supervised aerobic exercise programme (60-minute high intensity exercise sessions three times a week for 16 weeks supervised by experienced physiotherapists) or a control group. The primary outcome measure was change in cognitive performance estimated by the Symbol-Digit Modalities Test (SMDT). Secondary outcomes were neuropsychiatric and depressive symptoms, activities of daily living, quality of life and other cognitive measures. No significant difference was found between the intervention and control group on the primary outcome, but there was a significant difference in neuropsychiatric symptoms in favour of the intervention group. In a per protocol analysis (defined as attendance > 80% and exercise intensity > 70% of maximal heart rate), there was a significant effect on the primary outcome in favour of the intervention group, suggesting a dose-response relationship between moderate to high intensity exercise and cognition. In addition, people who participated in the exercise programme improved in physical fitness, physical function, dual-task performance and exercise self-efficacy. This study offered preliminary findings that high intensity aerobic exercise can postpone decline in cognition and reduce neuropsychiatric symptoms in patients with Alzheimer's disease.

Preliminary results from a community-based RCT, the Alzheimer's Disease Exercise Program Trial (ADEPT), indicate that participants who were randomised to six months aerobic exercise (150 minutes a week) showed reduced hippocampal atrophy rate on neuroimaging compared to those in the control arm, suggesting that aerobic exercise may moderate neurodegenerative processes in early Alzheimer's disease.[29] The full findings have yet to be published.

Promoting physical activity in older adults

The Irish National Dementia Strategy recommends engaging those with known cognitive impairment in

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public health promotion strategies and addressing physical inactivity as a modifiable risk factor. Some experts believe supervised exercise classes should become part of the standard of care for people with cognitive problems, as patients may not be equipped with the necessary knowledge and tools to exercise at the correct frequency and intensity without the guidance of an exercise professional. This begs the question, when prescribing exercise to those with a diagnosis or 'at risk' of cognitive impairment, how best to engage people to bring about meaningful health behaviour change? If exercise is established as an evidenced-based intervention for prevention of dementia, public health and community programmes will need to be funded to provide the access and resources for people at risk and those with symptomatic disease.

In 2016, two reports entitled *National Physical Activity Plan for Ireland*[31] and the Royal College of Physicians of Ireland's *Physical Activity: a prescription for a wonder drug*[32] were published. Both reports feed into national and international health strategies that have an overarching aim to make Ireland more physically active as a nation.

Related to these strategies, the National Exercise Referral Framework was also published recently.[33] This new framework recognises exercise as an effective targeted intervention in many chronic diseases, including dementia, and would give general practitioners in Ireland the opportunity to refer patients to structured supervised exercise programmes. The feasibility of the proposed framework as a national model and the sustainability of the funding model still need to be established prior to roll out.

Conclusions

Exercise has demonstrated some positive findings in recent RCTs and must be considered a plausible treatment strategy for mild cognitive impairment, Alzheimer's disease and other dementias. A considerable amount of attention was garnered by the recent findings of the FINGER study,[19] a large double-blind RCT that demonstrated a multi-domain intervention (diet, exercise, cognitive training, vascular risk monitoring) could improve or maintain cognitive functioning in at-risk older people from the general population. This adds strong support to a multi-modal approach to prevention strategies for Alzheimer's disease, but understanding the effect of each intervention in isolation first needs to be established.

The findings from recent studies discussed in this clinical review suggest that exercise can impact Alzheimer's-related changes in the brain at all stages of the disease. There is a growing body of evidence that suggests exercise may boost cognition and reduce neuropsychiatric symptoms, even in symptomatic disease. For aerobic exercise in particular, the field is standardising methods and focusing on the most appropriate dose of exercise to prescribe. It appears that the duration and intensity of an exercise intervention are crucial to determining its cognitive effect.

From the evidence gathered, it is imperative that the appropriate exercise prescription dose (a high intensity and up to six months in duration) is achieved to elicit a cognitive response in a mild cognitive impairment or Alzheimer's disease patient population.

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Appendix IV: Joint Research and Ethics Committee Approval from St. James's Hospital / Tallaght Hospital

THIS NOTEPAPER MUST NOT BE USED FOR PRESCRIPTIONS OR INVOICING PURPOSES

SJH/AMNCH Research Ethics Committee Secretariat
Claire Hartin Ph: 4142199
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Ms. Kate Devenney
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Dublin 2

11th January 2016

RE: The Effects of an Extensive Exercise Programme on the Progression of Mild Cognitive Impairment (MCI)

REC Reference: 2016 – 01 List 1 (3)
(Please quote reference on all correspondence)

Dear Ms. Devenney,

Thank you for your recent email correspondence and attachments which you sent to the SJH/AMNCH Research Ethics Committee requesting approval of an amendment to the above referenced study.

The Chairman, on behalf of the Research Ethics Committee, has reviewed your submission and the documents included and has given ethical approval to this amendment.

Yours sincerely,

Claire Hartin
Secretary
SJH/AMNCH Research Ethics Committee

NSV Code: WPA 00486

Appendix V: Ethics Committee Approvals from Mater Misericordiae University Hospital, St. Patrick's University Hospital, St. Vincent's University Hospital

Mater Misericordiae University Hospital
Sisters of Mercy
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Not for prescription purposes

Dr Cora McGreevy
Consultant Physician in Acute and Geriatric Medicine
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08th August 2016 Our Ref: 1/378/1837

RE: The Effects of an Extensive Exercise Programme on the Progression of Mild Cognitive Impairment (MCI)
Protocol Version: Version II, Draft IV Date: 14.12.2015
NeuroExercise Patient Information Leaflet, Version 2.0 29/06/2016
NeuroExercise Consent Form, Version 2.0 29/06/2016
Study Information Leaflet for Patient
Information for Healthcare Professionals
GP Letter
Poster
Sub-study
The Effects of Acute Exercise on Cognitive Function in Individuals with Mild Cognitive Impairment (MCI)
Protocol, Version number: 1.0 Date: 14/12/2015
NeuroExercise Referral Letter, Version 1.0
NeuroExercise Patient Information Leaflet, Version 1.0
NeuroExercise Consent Form, Version 1.0
Poster

Dear Dr McGreevy

I acknowledge receipt of your correspondence dated 29th June 2016 addressing points of clarification and enclosing the Site Signature & Delegation of Authority Log, revised NeuroExercise Patient Information Leaflet (Version 2.0 29/06/2016) and revised NeuroExercise Consent Form (Version 2.0 29/06/2016) as requested by the Mater Misericordiae University Hospital and Mater Private Hospital Research Ethics Committee for the above research study to be carried out at the Mater Misericordiae University Hospital (MMUH).

This correspondence has been noted and the revised documents have been approved. Approval to proceed with this research study at the MMUH is granted; this approval is valid until 23rd June 2018.

It is your responsibility to adhere to the approved study protocol and ensure that all investigators involved with the research only use the approved documents without deviation (unless they have been approved by the Research Ethics Committee), to submit annual reports setting out the progress of the research (giving details of the number of participants who have been recruited, the number who have completed the study and details of any adverse events etc.) and to notify the Research Ethics Committee when the research is concluded.

The Mater Misericordiae University Hospital and Mater Private Hospital Research Ethics Committee would like to remind all investigators involved in research of their legal obligations under the law on Data Protection.

Yours sincerely

Prof Malcolm Kell
Chairman
Research Ethics Committee

c.c. Ms Kate Devenney , PhD Candidate, Discipline of Physiotherapy, Trinity College Dublin

PRIVATE & CONFIDENTIAL

June 8th, 2016

Ms Kate Devenney
Research Physiotherapist
Trinity Health Sciences Building
St James's Hospital
Dublin 8
(devennek@tcd.ie)

Re: The Effects of an Extensive Exercise Programme on the Progression of Mild Cognitive Impairment (MCI)
PhD sub-study: The Effects of Acute Exercise on Cognitive Function in Individuals with Mild Cognitive Impairment (MCI)
(Protocol 08/16)

Dear Ms Devenney,

Your application was considered at the Research Ethics Committee (REC) meeting held on **June 7th, 2016**, in the Conference Room at St Patrick's University Hospital.

Your application was granted full ethical approval by the following committee members who were in attendance at this meeting:

Mr Terence Coghlan	Ms Marie Therese Mulholland
Ms Jennifer Donnelly	Dr Bré Sullivan
Mr Andreas Heil	Ms Marie Tuohy
Dr Emer Keeling	Prof. John Waddington
Prof. Jim Lucey	

Approval was granted subject to the following standard conditions:

1. You must adhere fully to the terms and conditions set out in your research protocol.

2. All persons involved in this research who are not employees of St Patrick's Mental Health Services are required to obtain an honorary contract from the hospital. This process should be initiated by your study supervisor. It will be your responsibility to ensure that these contracts are renewed and kept up-to-date as necessary throughout the duration of your study.

3. If there are any material changes to be made to Protocol 08/16 in the next 12 months, you must contact the Research Ethics Committee for approval.

4. You must report back to the Research Ethics Committee no later than 12 months subsequent to this approval letter (June 8th, 2017), with a summary report on the progress of this research. This report can be downloaded from the hospital website. Failure to complete this report may result in ethical approval being withdrawn for your research.

5. The committee encourages all researchers to publish the results of their study once it is completed, whether these appear to be positive or negative.

6. Please complete the attached form and send it via email to regionallibrary@hse.ie. The Directorate of Clinical and Quality Care in the HSE have requested that details of all research projects in Ireland be pooled together in one location, namely, www.lenus.ie, for the purpose of promoting a culture of research and in order to deliver evidence based clinical care. The HSE hope to gain a complete picture of the quality and quantity of healthcare and healthcare-related research in Ireland, and St. Patrick's Mental Health Services have agreed to cooperate with this process. This repository of research activity is managed by Health Librarians based in Dr Steevens' Hospital, and we thank you in advance for emailing this relatively simple form to them at your convenience.

Just one additional detail was requested from the committee. They were interested in knowing who performs the medical examination? Is it one of the researchers or someone totally independent of the study? Please could we ask you to respond to this question before the end of this month?

We wish you well in your research.

With very best wishes.
Yours sincerely,

JAMES V. LUCEY MD., Ph.D., FRCPI., FRCPsych.
Secretary to the Research Ethics Committee | Medical Director
Medical Council 00646

Encl.

cc. *Prof. Declan McLoughlin, Consultant Psychiatrist*

St. Vincent's Healthcare GROUP LIMITED

Ethics and Medical Research Committee
ELM PARK, DUBLIN 4
Tel. (01) 2214117 Fax (01) 2214428
email: joan.mcdonnell@ucd.ie or jacinta.mcmanus@ucd.ie

8th June, 2016.

Dr. J. Kinsella,
Consultant Neurologist,
St. Vincent's University Hospital,
Elm Park,
Dublin 4.

Re:- The Effects of an Extensive Exercise Programme on the Progression of Mild Cognitive Impairment(MCI). The Effects of Acute Exercise on cognitive Function in Individuals with Mild Cognitive Impairment (MCI). Checklist. Standard Application Form Version 1.0 19/4/2016. PIL/Consent Version 1. Letter to Physiotherapy Department, SJH Version 1. Patient Letter Version 1. NeuroExercise Referral Letter Version 1.0 27/4/2016. Trail Making Test Part A. Trail Making Test Part B. PAL. STROOP Neuropsychological Screening Test Record Form. Form C Responses – Color Task. Appendix D SART. DEMQOL Version 4. Appendix F DAD. Appendix G CES-D. Appendix H General Self-Efficacy Scale. Borg's Rating of Perceived Exertion (RPE) Scale. LAPAQ. PSQI. NEO-FFI (English). SOP for management of ECG changes of Exercise Testing. SOP for Blood Pressure Evaluation. Insurance Certificate. Study Information Leaflet. Information for Healthcare Professionals. Poster. Main Study Protocol Version II, Draft 4 date:14/12/2015. Sub- study Protocol Version 1.0 14/12/2015.

Dear Dr. Kinsella ,

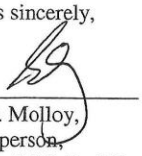
Thank you for attending the Ethics and Medical Research Committee meeting held on Wednesday 1st June, 2016 at which the above study was reviewed. This study was granted provisional ethical approval pending the following:

1. Clarification is required if an interim data analysis at 6 months will be performed.
2. Clarification is required if having had an MRI is a mandatory inclusion criteria.
3. In the application form, the response to C 1.1 should be revised to recruitment will only take place in outpatient clinics and not through databases.
4. In the PIL under Volunteer 3rd paragraph should include the requirement to wear the activity monitor for 1 week.
5. The PIL should include a statement that the participants will not get any feedback until the study is completed.

Please note: Prior to this study being granted full ethics committee approval the following documentation in hard copy will be required for chairman's review.

- A covering letter addressing each of the above points.
- A clean and tracked change copy of all revised documentation with the footer version and date revised.

Yours sincerely,



Dr. E. Molloy,
Chairperson,
Ethics & Medical Research Committee

Appendix VI: Study Patient Information Leaflet and Consent Form

OSPIDÉAL NAOMH SÉAMAS
ST. JAMES'S HOSPITAL

Ospidéal Naomh Séamas, Sráid Shéamais, Baile Átha Cliath 8.
St. James's Hospital, James's Street, Dublin 8.
+ 353 1 410 3000 www.stjames.ie

Patient Information Leaflet

Study Title:

(1) The effects of an extensive exercise program on the progression of Mild Cognitive Impairment (MCI)

(2) The effects of acute exercise on cognitive function in individuals with Mild Cognitive Impairment (MCI)

Sponsor: Health Research Board

Principal Investigators:	Professor Brian Lawlor Dr Emer Guinan
Research Physiotherapist:	Kate Devenney
Study Doctor:	Professor Brian Lawlor
Site Address:	St James's Hospital, Dublin

This is a clinical study, a type of research study. The Research Team will explain the clinical study to you. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

1. Why is this study being done?

Mild cognitive impairment is characterised by deficits in memory and thinking skills that does not significantly impact day-to-day function. To help ensure an aging society live enjoyable and productive life, research into treating conditions such as Alzheimer's disease, and other forms of age-related diseases, is an urgent public health priority. The purpose of this study is to investigate the effect of a 12 month exercise programme in patients who have mild cognitive impairment. The exercise programme is testing the theory that exercise may prevent the progression of cognitive decline (decline in the mental processes of perception, memory, judgement and reasoning) in patients with mild cognitive impairment.

2. Why am I being asked to take part?

People who have attended the memory clinic at St. James's Hospital with a diagnosis of Mild Cognitive Impairment are being asked to participate.

3. Do I have to take part?

No, it is up to you to decide whether or not you take part.

If you decide to take part, you will be asked to sign the consent form. You will be given a copy of this information sheet and a signed consent form for you to keep.

You will still be free to leave the study at any time, with or without giving a reason. If you decide to leave the study, this will not affect your future treatment and care.

4. How many people will take part in the study?

Approximately 75 people will take part in this study, in St James's Hospital, Dublin. An additional 150 people will take part in the study which is also being conducted in two other European centres.

The study will last approximately two years and your participation will last for 12 months.

5. What will happen to me if I take part?

You will be invited to participate in this programme when your doctor has indicated to the research team that you are medically well and able for the interventions involved and you clear the screening criteria.

There will be 3 different groups involved in the study. If you choose to take part in the study, you will be "randomised" into one of the study groups. Randomisation means that you are put into a group by chance. A computer program will place you in one of the 3 study groups. Neither you nor your doctor can choose the group you will be in. One group will act as the "control group" and will not participate in the exercise programme. If you are selected to be in the "control" group, you will be required to attend for assessments at the Clinical Research Facility at St. James's Hospital as detailed below.

The exercise groups will both undertake a 12 month supervised and home based exercise programme. One group will complete a stretching and toning programme. The other group will complete an aerobic exercise programme (examples of aerobic exercise include cycling and walking). These interventions will be provided in addition to your usual medical care provided at St. James's Hospital.

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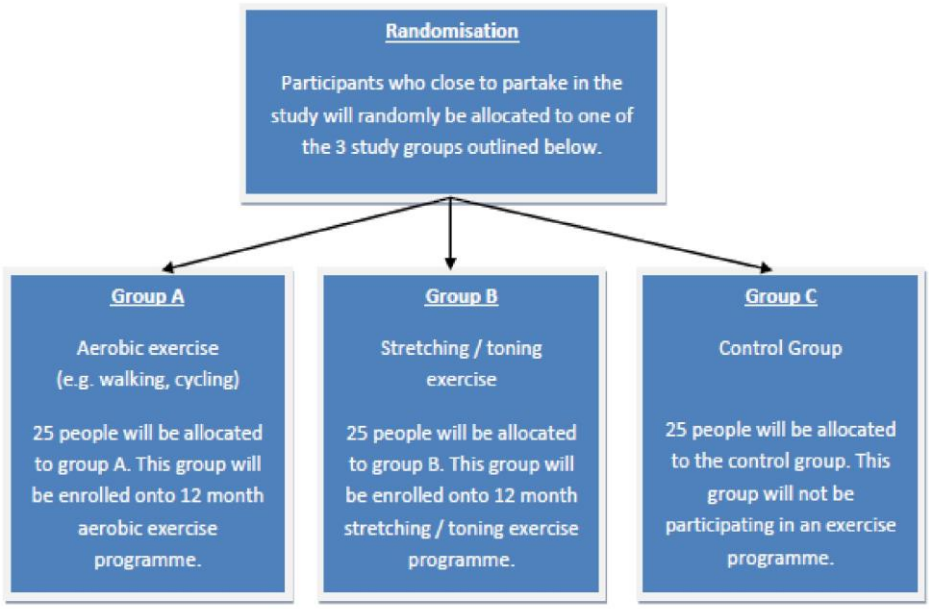
St. James's Hospital, James's Street, Dublin 8.
+ 353 1 410 3000 www.stjames.ie



The aim of this study is to deliver a 12 month exercise programme (3 exercise sessions per week. This equals 56 supervised and 88 unsupervised/home based exercise sessions in total) for patients with mild cognitive impairment. The supervised exercise sessions will take place at the Clinical Research Facility in St. James's Hospital. The unsupervised exercise sessions will be completed at home and you will wear a monitor to record your activity. Each exercise session will last approximately 1 hour.

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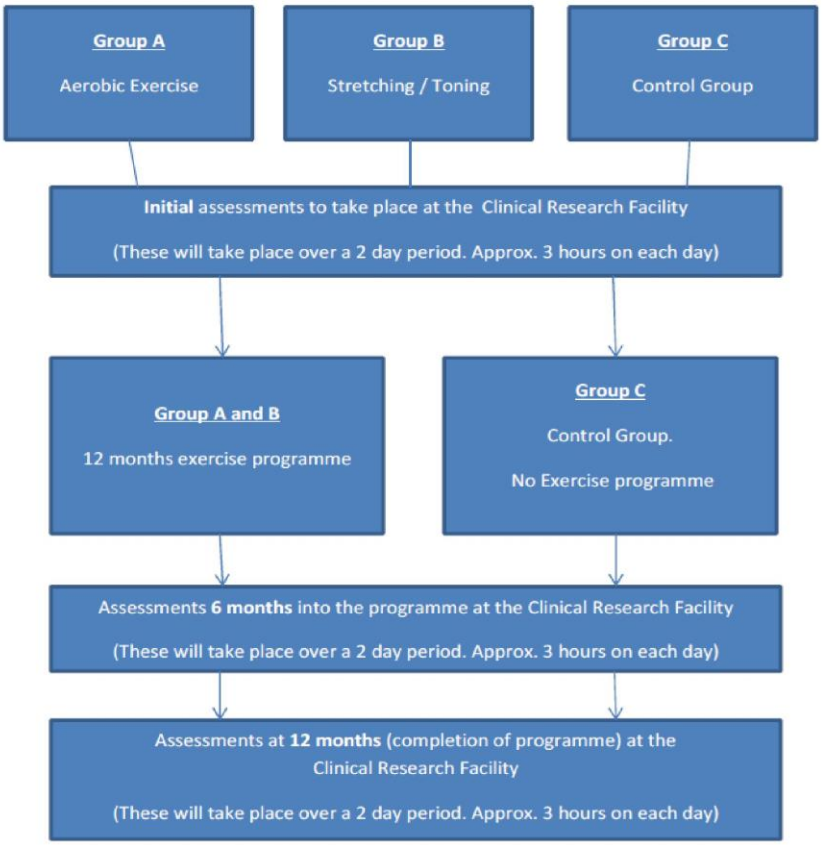
St. James's Hospital, James's Street, Dublin 8.
+ 353 1 410 3000 www.stjames.ie

If you decide to participate in the study, you will be assessed by the research team at three time points:

- prior to commencing the exercise programme (0 months)
- six months into the exercise programme (at 6 months)
- upon completion of the exercise programme (at 12 months)



The second study will examine the effects of single bouts of exercise on cognitive function in individuals with Mild Cognitive Impairment (MCI). Prior to exercise testing, participants will be randomised to group A or B. You will have the similar testing done, in differing order. Blood samples and tests of your cognitive function will be obtained around the exercise testing.

Participants who are randomly selected to one of the exercise groups will have blood tests and tests of their cognitive function during week 1, 6 and 12 of their exercise programme. Blood samples and cognitive tests will be performed on each of these time points prior to the supervised exercise class in the CRF in St. James's Hospital. The bloods and cognitive tests will then be repeated after the exercise session.

Details of the initial assessments are detailed below.

Vital signs: Heart rate, blood pressure and oxygen saturation will be recorded at the screening visit and prior to commencing all supervised exercise sessions
Body composition: Weight and height will be recorded at initial assessment
Medical examination: all participants will undergo a medical examination by a doctor prior to completing exercise testing

The following assessments will be completed at 0, 6 and 12 months during the study period.
These assessments will take place over a 2 day period. It will take approximately **3 hours on each day** to complete assessment.

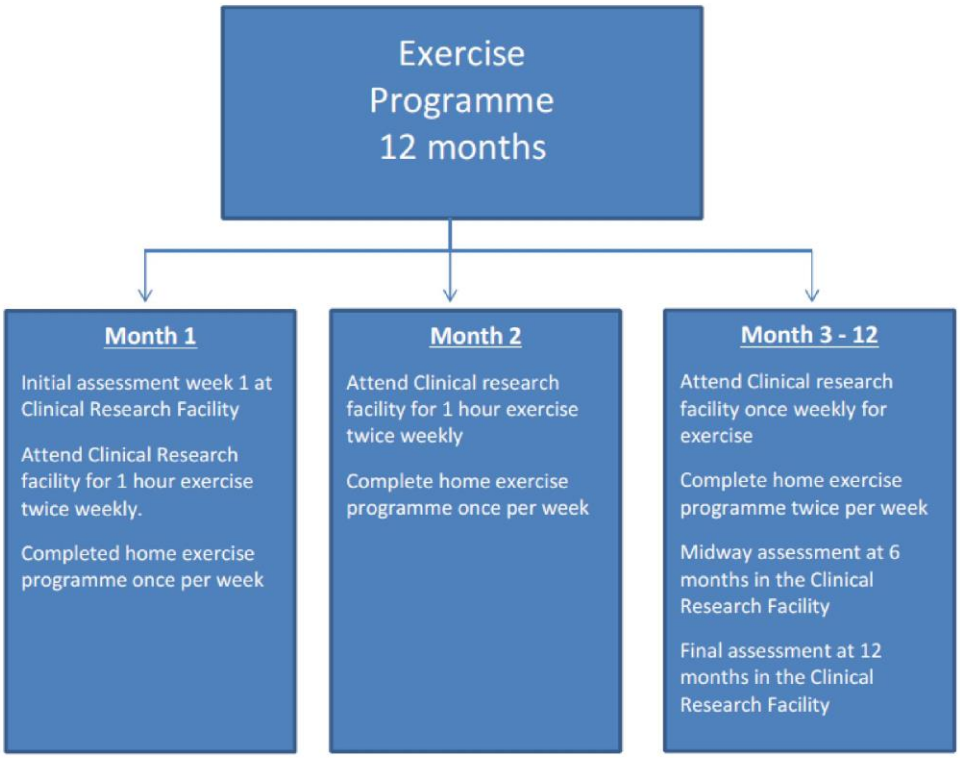
- **Cognitive performance** will be measured by a number of tests that test attention, memory and ability to perform certain tasks
- You will be required to complete 7 separate **Questionnaires** pertaining to:
    a. quality of life
    b. physical activity
    c. ability to carry out activities of daily living
    d. depression
    e. Sleep quality
    f. personality traits
    g. behavioural traits
- We will record your **Blood pressure** when you move from a lying position into sitting and then standing
- An **exercise test** will be carried out to assess your physical fitness**.** During the exercise test, you may experience general fatigue and shortness of breath
- You will be given a **physical activity monitor** to wear at home for a week at the three assessment time points
- A **blood sample** will be obtained for analysis – about 3 teaspoons of blood every time blood is taken.
- You will be required to complete 3 **physical assessments** to ascertain your general strength, endurance, mobility and balance

If you exit the study prior to completing the 12 months of exercise, you will be invited to complete an exit assessment with the research team. The exit assessment will be optional; you may choose to decline completing the exit assessment.

6. What will I have to do?

If you are in the control group, you will attend the Clinical Research Facility at 0, 6 and 12 month time points to undergo assessments. You will not be involved in the exercise programme detailed below. You will receive a newsletter in the post every 3 months to keep you updated on how the trial is progressing. You will be contacted by phone every 2 months by a member of the research team to check how you are doing.

If you are enrolled in the exercise programme, you will need to attend the Clinical Research Facility at St James's Hospital for supervised exercise sessions over a 12 month period. Each exercise session will last approximately 1 hour. You will also have to complete exercise sessions at home. Please see diagram below for further details. Where possible, study appointments will be scheduled for a time that is convenient for you to attend.



7. What are the benefits of taking part?

There may or may not be direct benefits to people taking part in the study. The study aims to examine the effect of different exercise interventions in people with mild cognitive impairment. The results will help us establish if exercise interventions may be of benefit for people with mild cognitive impairment in the future.

8. What are the risks of taking part?

We do not anticipate adverse effects during the assessments or participating in the prescribed exercise intervention. The proposed exercise intervention has been designed in line with established protocols, thereby posing minimal risk.

Participation in the exercise intervention will be with the consent of your doctor and will be supervised closely by your physiotherapist. Your risk of adverse events will be minimised through thorough medical screening prior to exercise testing and monitoring during exercise intervention.

While rare, adverse events are possible. Serious adverse events may include: heart attack, stroke, unconsciousness or other serious injury.

You may feel a little tired after the exercise test and during the initial stages of the exercise intervention but we expect that you will recover quickly.

There is a risk of bruising or fainting when taking blood samples. If any results with potentially harmful consequences are discovered your team will be informed immediately.

9. Will I receive payment for being part of this study?

You will not be paid for taking part of this study. However, you will receive remuneration for car parking costs incurred while attending study assessments and exercise sessions at the Clinical Research Facility.

10. What happens if I get hurt taking part in this study?

All participants and professionals working on the study are covered by clinical indemnity insurance. This insurance covers any damage resulting from the research. For further details please contact Kate Devenney. Contact details are listed at the end of this document.

11. Will my information be kept private?

If you decide to take part in the study, you give the researchers permission to collect information about you and share it with the Health Research Board. Any information that identifies you (such as your name and address) will not be shared with the Health Research Board.

Your study data will be identified with a code number which will not include your name or other information that directly identifies you.

As this research project is taking place at 2 other research sites in Europe (Nijmegen, Netherlands and Cologne, Germany), information collected related to the study and some of the blood samples collected will be transferred to these sites to be pooled together centrally for analysis. The additional blood samples will be kept on site in St. James's Hospital.

Personal and medical information identifying you will be kept confidential. We will keep it in a secured file. At any time, you may ask to see your personal information.

Your study information will be used to determine the effect of a long term exercise programme on patients with mild cognitive impairment. The information gained will help inform the planning of future exercise programmes for people with mild cognitive impairment.

Your information will be kept on file for up to 15 years and will be destroyed securely after that time.

The results of the study may be used in presentations or be published in scientific reports. You will not be identified in any presentation or publication.

To make sure the data collected during the study is correct and accurate, it may be checked by researchers, representatives of Trinity College Dublin or the Health Research Board, external auditors or inspectors or members of the Ethics Committee. They will keep your information confidential. By signing consent, you are agreeing to allow such access.

12. Who should I contact if I have any questions?

For more information or answers to your questions about the study please contact any member of our research team, Monday – Friday from 9.00 am to 5.00pm.

Research Team Contact Details	
Kate Devenney, Research Physiotherapist	01-8963613
Dr. Emer Guinan, Principal Investigator	01-8964809

13. Has this study been approved?

Yes, this study has been reviewed and approved by the AMNCH/SJH Research Ethics Committee (Approval reference number 2015/09/04).

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+ 353 1 410 3000 www.stjames.ie

Consent Form

Study Title:
1. The effects of an extensive exercise programme on the progression of Mild Cognitive Impairment
2. The effects of acute exercise on cognitive function in individuals with Mild Cognitive Impairment

Sponsor: Health Research Board

Principal Investigator	Professor Brian Lawlor Dr Emer Guinan
Research Physiotherapist:	Kate Devenney
Study Doctor:	Professor Brian Lawlor
Site Address:	St James's Hospital, Dublin

Please tick each box to confirm you have read, understood and agreed to each of the points in this form.

1. I have read and understood the Patient Information Leaflet, Version __, dated _____. I have had time to consider it and the opportunity to ask questions.	☐
2. I understand that my taking part is voluntary and that I am free to withdraw at any time, without giving a reason and without my medical care or legal rights being affected. If I withdraw, I understand that my data can still be used up to when I withdrew, unless I state otherwise.	☐
3. I understand that my medical records may be looked at by authorised personnel from Health Research Board, the ethics committee, the regulatory authority, where it is relevant to my taking part in this study. I give my permission for such personnel to have access to my records. I understand that if I withdraw from the study, my records may need to be accessed in order to verify data collected while I was still in the study.	☐
4. I understand what will happen to my blood/tissue samples and I consent to the retention of my biological samples for research purposes.	☐
5. I consent to the collection and use of personal and sensitive information about me, including medical information, which will not include my name.	☐

6. I agree to the use of data collected in this study to be used in future studies without the need for giving consent again.	☐
7. I agree to take part in this study	☐

Name of Patient (CAPITALS)	*Signature*	*Date (Day Month Year)*
Investigator Name (CAPITALS)	*Signature*	*Date (Day Month Year)*
Name of Person taking Consent (if different to Investigator)(CAPITALS)	*Signature*	*Date (Day Month Year)*

Appendix VII: Study Advertisement

Exercise and Dementia Prevention study

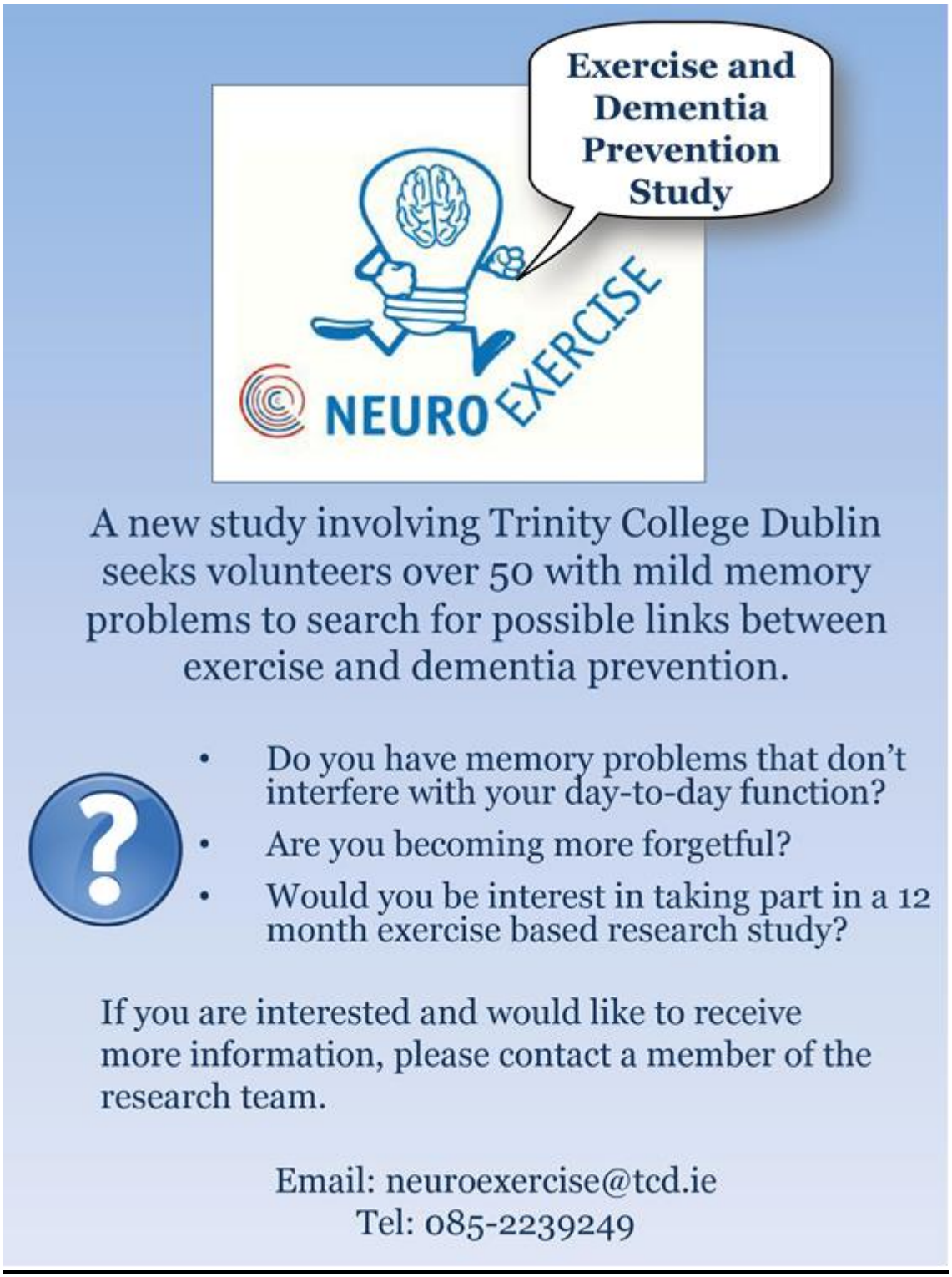
A new study involving Trinity College Dublin seeks volunteers over 50 with mild memory problems to search for possible links between exercise and dementia prevention.

- Do you have memory problems that don't interfere with your day-to-day function?
- Are you becoming more forgetful?
- Would you be interested in taking part in a 12 month exercise based research study?

Potential participants will be screened over the phone initially and may then be invited to attend a study screening clinic. If you are interested and would like to receive more information, please contact a member of the research team.

Email: Neuroexercise@tcd.ie
Phone: 085-2239249

Appendix VIII: Study Poster



Appendix IX: Home Exercise Diary

Home Exercise Log Book

The purpose of this log book is to help us accurately record how much exercise and activity you are doing outside the classes. Please complete at home and bring to the classes.

You are encouraged to complete _____ additional 45 minute walking / exercise session at home every week.

At the back of the diary you will find a BORG scale. You should use this as a reference to help you exercise to the correct intensity when completing home exercise sessions. You should be aiming to achieve a BORG score of _____.

Name: _____

Home Exercise Log Book

Date	**Type of activity** *(running, cycling, walking..)*	**Time/extent** *(minutes, hours, meters)*	***Perceived Exertion Level*** (BORG 6 – 20) *(BORG scale)*	**Any additional comments** *(Pain, uncommon tiredness)*

Borg's Rating of Perceived Exertion (RPE) Scale

Perceived Exertion Rating	Description of Exertion
6	No exertion. Sitting & resting
7	Extremely light
8	
9	Very light
10	
11	Light
12	
13	Somewhat hard
14	
15	Hard
16	
17	Very hard
18	
19	Extremely hard
20	Maximal exertion

Appendix X: Absolute and Relative Indications for Stopping Exercise

Indicators for Stopping Exercise

Absolute indications for Stopping Exercise:
• Suspicion of a myocardial infarction or acute myocardial infarction (heart attack)
• Onset of moderate-to-severe angina (chest pain)
• Drop in systolic blood pressure (SBP) below standing resting pressure or drop in SBP with increasing workload accompanied by signs or symptoms
  ○ Hypotensive response resulting in SBP <60mmHg
• Signs of poor perfusion (circulation or blood flow) including pallor (pale appearance to the skin), cyanosis (bluish discoloration) or cold and clammy skin
• Severe or unusual shortness of breath
• CNS (central nervous system symptoms
  ○ Ataxia (failure of muscular coordination)
  ○ Vertigo (an illusion of dizzying movement)
  ○ Visual or gait (pattern of walking or running) problems
  ○ Confusion
• Patient's request to stop
• Irregular pulse
• Extreme fatigue

Relative Indications: • Increasing chest pain • Physical or verbal manifestations of shortness of breath or severe fatigue • Wheezing • Leg cramps or intermittent claudication (grade 3 on a 4-point scale) • Hypertensive response

Appendix XI: Borg's Rating of Perceived Exertion

Borg's Rating of Perceived Exertion (RPE) Scale

Perceived Exertion Rating	Description of Exertion
6	No exertion. Sitting & resting
7	Extremely light
8	
9	Very light
10	
11	Light
12	
13	Somewhat hard
14	
15	Hard
16	
17	Very hard
18	
19	Extremely hard
20	Maximal exertion

Appendix XII: Case Report Form Baseline Assessment

Participant No:_____
Week _____

Baseline Assessment T0 Visit 1

Medical chart obtained: ☐

Explain study: ☐ Date of Birth _____

Past Medical History (include alcohol, smoking Hx):

Medications:

_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____

Social History (include education in years and baseline exercise):

Signed: **Date:**

1

Participant No:_____
Week _____

Eligibility criteria

Do you have a history of any of the following?

Epilepsy / Seizures	Yes	☐	No	☐
Stroke	Yes	☐	No	☐
Significant Head injury / LOC	Yes	☐	No	☐
Any neurological condition	Yes	☐	No	☐
Heart attack	Yes	☐	No	☐
Heart failure	Yes	☐	No	☐
Carotid stents	Yes	☐	No	☐
High blood pressure	Yes	☐	No	☐
Diabetes	Yes	☐	No	☐
Lung, liver, kidney disease	Yes	☐	No	☐
Alcohol problem	Yes	☐	No	☐
Drug problem	Yes	☐	No	☐
Vitamin B12 deficiency	Yes	☐	No	☐
Hypothyroidism	Yes	☐	No	☐
Mental health (e.g schizophrenia, manic depression)	Yes	☐	No	☐

If yes to any of the above, please give details

_____

_____

_____

_____

Verified that participant meets the above inclusion and exclusion criteria ☐

Signed: **Date:**

Participant No:_____
Week _____

Consent form signed and copy given to participant: ☐

Verbal consent to GP letter: Yes ☐ No ☐

MoCA score ☐ ***Remember to adjust for education. Add 1 point to total score if 12 or less years of education**

Randomise to schedule A or B prior to exercise testing ☐

Procedures to be completed prior to exercise testing:

GROUP A		**GROUP B**	
Baseline blood sampling x 2 (5ml) serum (red) x 3 (3ml) plasma (purple)*		Baseline blood sampling x 2 (5ml) serum (red) x 3 (3ml) plasma (purple)*	
Baseline cognitive testing - Paired Associates Learning - SART - Stroop Task		Baseline cognitive testing - Paired Associates Learning - SART - Stroop Task	
Resting Vital signs and ECG		30 minutes seated rest	
Exercise testing as per protocol (with prior medical clearance and test supervision)		Control blood sampling x 2 (5ml) serum (red) x 1 (3ml) plasma (purple)	
		Control cognitive testing	
		Resting Vital signs and ECG*	
		Exercise testing as per protocol	

* x2 plasma samples taken during baseline blood sampling are for epigenetics analysis. These samples should be placed directly into the fridge and transferred to -80° as soon as possible .Tube labelling instructions for these samples :

IRE_4_1a and IRE_4_1b are the two samples from participant number 4 collected at T0 (before intervention) in Ireland.

IRE_4_2a and IRE_4_2b are the two samples from participant number 4 collected at T2 (after intervention) in Ireland.

The additional samples will be stored in the CRF fridge and transferred to the lab following completion of assessment.

Participant No:_____
Week _____

Resting Vital Signs
Blood Pressure and Heart Rate

Weight _____ kg Height _____ cm

	BP (Seated R arm)	BP (Seated L arm)	BP (Standing)	HR	% Sp02
Pre Ex Test					

The remainder of this section is to be completed by **supervising doctor**.

Resting ECG
(Collect strip)

Safe to proceed with CPET Yes ☐ No ☐ (If no please comment below)

Additional Comments:

_____
_____
_____
_____

Signed: **Date:**

Print Name:

Participant No:_____
Week _____

CPET recording as per WHO protocol. The test will commence with 3 minutes rest followed by the incremental phase of exercise during which the load will increase by 25W every 2 minutes until the test in terminated.

Time (mins)	Power (watts)	RPM	Heart Rate	Blood Pressure	BORG	Lactate
0						
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						

The test will terminate when three out of 4 of the following criteria are to be met:

- Clinical signs of exhaustion,
- RER >= 1.10,
- Test finishing within 10 beats of the predicted heart rate (=220-age)
- Flattening of the VO2 uptake curve (<= 110 ml increase during the last minute)

Participant No:_____
Week _____

Recovery:
Participants should cool down by cycling unloaded for 3 minutes

	HR	BP	Sa02
1 min			
3 min			
10 min			

Post exercise ECG

Testers **1.**_____

2._____

Post Exercise testing procedures to be complete:

GROUP A		**GROUP B**	
Post Ex blood sampling x 2 (5ml) serum (red) x 1 (4ml) plasma (purple)		Post Ex blood sampling x 2 (5ml) serum (red) x 1 (4ml) plasma (purple)	
Post Ex cognitive testing - Paired Associates Learning - SART - Stroop Task		Post Ex cognitive testing - Paired Associates Learning - SART - Stroop Task	
Ensure all blood samples labelled		Ensure all blood samples labelled	
Labelled samples:		Labelled samples:	

Participant No:_____
Week _____

ST. JAMES'S HOSPITAL

Baseline Assessment T0 Visit 2

Neuropsychological testing:

1. DemQol		
2. Trail Making Test A + B		
3. Verbal fluency (letters + animals)		
4. Cogstate		

Secondary outcomes:

Timed up and Go (Practice test first before timed trial)		Time taken to complete in seconds _____
Hand Grip Strength (3 trials each hand, 1 minute rest between trials, record best score)		Right **1.** _____ **2.** _____ **3.** _____ Left **1.** _____ **2.** _____ **3.** _____
30 Second Chair Stand (Complete 2 practice stands before starting timed test)		Number of completed stands: _____

Additional questionnaires:

Pittsburgh Sleep Quality Index		
General Self Efficacy Scale		
LAPAQ		

Questionnaires to be completed at home and collected week 1 of exercise:

NEO-FFI		
CES-D		

Physical Activity Monitor	

Participant No:_____
Week _____

Randomisation

Group _____

Additional Comments:

_____

_____

Signed: **Date:**

Appendix XIII: Case Report Forms Exercise Classes

Exercise Class No _____ **Week** _____

Study Number _____

Target HR = _____

Verbal consent to participate in class: ☐

Subjective Report:

_____

_____

Blood Pressure and Heart Rate

Pre Exercise: _____/____mmHg _____bpm

Post Exercise: _____/____mmHg _____bpm

Pre-exercise stretching: March on the spot, arm swings, shoulder rolls, elbow-flexes, wrist turns, knee flexes and ankle pumps ☐

	Time	Intensity	bpm	Mode	Completed (√)
Warm up					
Aerobic Component					
Cool Down					

Post exercise stretching: ☐

No adverse effects to exercise class: ☐

Was requested participant to complete _____ additional exercise session, as per above intensity and duration, as part of home exercise plan this week.

Additional Comments:

_____

_____

Signed: **Date:**

1

Exercise Class No _____ **Week** _____

Study Number _____

Target HR = _____

ST. JAMES'S HOSPITAL

Verbal consent to participate in class: ☐

Subjective Report:

_____

_____

Pre-exercise stretching (Warm up): March on the spot, arm swings, shoulder rolls, elbow-flexes, wrist turns, knee flexes and ankle pump ☐

Non-aerobic exercise	Time	BORG RPE	Completed (√)

Post exercise stretching and cool down: ☐

No adverse effects to exercise class: ☐

_____ additional exercise session(s), were completed as part of home exercise plan this week.

Additional Comments:

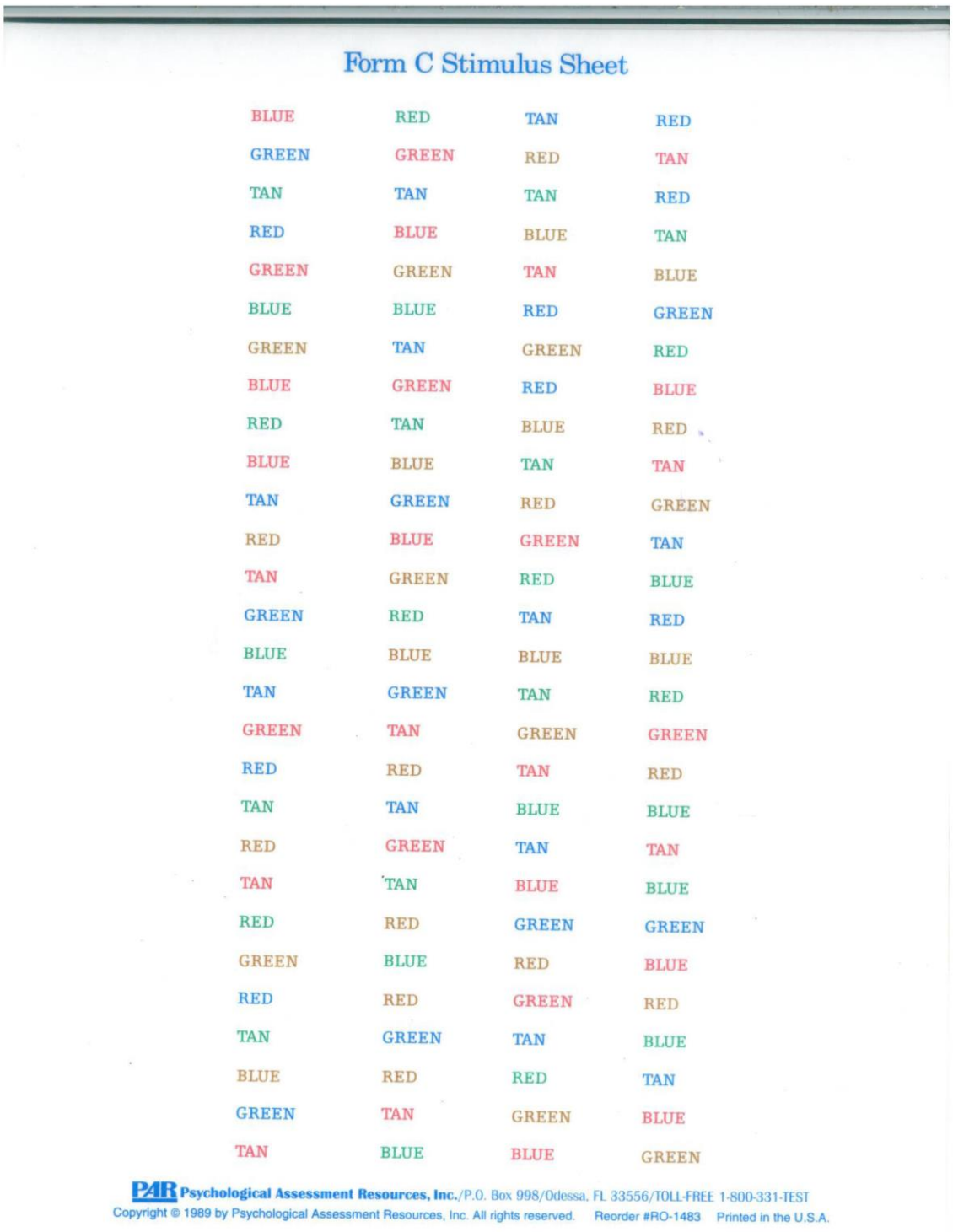
_____

_____

Signed: **Date:**

2

Appendix XIV: Stroop Colour Stimulus Sheet and the Colour-Word Stimulus sheet



Form C Stimulus Sheet

BLUE	RED	TAN	RED
GREEN	GREEN	RED	TAN
TAN	TAN	TAN	RED
RED	BLUE	BLUE	TAN
GREEN	GREEN	TAN	BLUE
BLUE	BLUE	RED	GREEN
GREEN	TAN	GREEN	RED
BLUE	GREEN	RED	BLUE
RED	TAN	BLUE	RED
BLUE	BLUE	TAN	TAN
TAN	GREEN	RED	GREEN
RED	BLUE	GREEN	TAN
TAN	GREEN	RED	BLUE
GREEN	RED	TAN	RED
BLUE	BLUE	BLUE	BLUE
TAN	GREEN	TAN	RED
GREEN	TAN	GREEN	GREEN
RED	RED	TAN	RED
TAN	TAN	BLUE	BLUE
RED	GREEN	TAN	TAN
TAN	TAN	BLUE	BLUE
RED	RED	GREEN	GREEN
GREEN	BLUE	RED	BLUE
RED	RED	GREEN	RED
TAN	GREEN	TAN	BLUE
BLUE	RED	RED	TAN
GREEN	TAN	GREEN	BLUE
TAN	BLUE	BLUE	GREEN

Form C-W Stimulus Sheet

BLUE	GREEN	RED	GREEN
GREEN	BLUE	GREEN	TAN
RED	RED	BLUE	RED
TAN	BLUE	TAN	TAN
GREEN	TAN	RED	BLUE
BLUE	RED	TAN	TAN
RED	GREEN	BLUE	GREEN
TAN	TAN	TAN	RED
RED	GREEN	RED	GREEN
BLUE	BLUE	BLUE	RED
RED	RED	RED	BLUE
TAN	TAN	TAN	GREEN
BLUE	GREEN	BLUE	TAN
TAN	RED	GREEN	BLUE
RED	BLUE	TAN	GREEN
BLUE	GREEN	BLUE	RED
GREEN	RED	TAN	GREEN
TAN	GREEN	BLUE	TAN
GREEN	BLUE	RED	GREEN
TAN	TAN	GREEN	BLUE
RED	GREEN	BLUE	TAN
BLUE	RED	GREEN	BLUE
RED	TAN	BLUE	GREEN
TAN	BLUE	GREEN	RED
RED	TAN	RED	BLUE
TAN	RED	GREEN	GREEN
GREEN	TAN	TAN	RED
TAN	GREEN	RED	BLUE

PAR Psychological Assessment Resources, Inc./P.O. Box 998/Odessa, FL 33556/TOLL-FREE 1-800-331-TEST

Appendix XV: Search Terms in Systematic Review

EMBASE

('mild cognitive impairment'/exp or 'cognitive defect'/exp) AND 'exercise'/exp AND ('mental function'/exp OR 'cognition assessment'/exp OR 'arousal'/exp OR 'task performance'/exp OR 'perception'/exp OR 'therapy effect'/exp OR 'outcome assessment'/exp OR 'neuropsychological test'/exp)

(Cogniti* NEAR/2 (impairment OR defect)):ti,ab

(exercise NEAR/2 (acute OR intense OR 'single bout' OR test OR chronic)):ab,ti

PubMed

("Cognition Disorders"[Mesh:NoExp] OR "Mild Cognitive Impairment"[Mesh]) AND ("Exercise"[Mesh] OR "Exercise Therapy"[Mesh] OR "Physical Fitness"[Mesh]) AND ("Mental Processes"[Mesh] OR "Task Performance and Analysis"[Mesh] OR "Outcome and Process Assessment (Health Care)"[Mesh] OR "Neuropsychological Tests"[Mesh])

Cochrane

[mh "Cognition Disorders"]

[mh "Mild Cognitive Impairment"]

#1 or #2

[mh "Exercise"]

[mh "Exercise Therapy"]

[mh "Physical Fitness"]

#4 or #5 or #6

[mh "Mental Processes"]

[mh "Outcome and Process Assessment (Health Care)"]

[mh "Task Performance and Analysis"]

[mh "Neuropsychological Tests"]

#8 or #9 or #10 or #11

#3 and #7 and #12

PsycINFO

DE "Cognitive Impairment" OR DE "Cognition" OR DE "Animal Cognition" OR DE "Mental Lexicon" OR DE "Cognitive Ability" OR DE "Memory Disorders"

DE "Exercise" OR DE "Physical Activity" OR DE "Physical Fitness"

DE "Brain Training" OR DE "Mathematical Ability" OR DE "Reading Ability" OR DE "Spatial Ability" OR DE "Verbal Ability" OR DE "Cognitive Ability" OR DE "Cognitive Appraisal" OR DE "Cognitive Assessment" OR DE "Physiological Arousal" AND DE "Cognitive Processes" OR DE "Executive Function" OR DE "Neuropsychological Assessment" OR DE "Attention" OR DE "Cognitive Control" OR DE "Set Shifting" OR DE "Perception" AND DE "Treatment Outcomes" OR DE "Treatment Effectiveness Evaluation"

CINAHL

(MH "Cognition Disorders") AND (MH "Exercise+" OR MH "Physical Fitness+" OR MH "Sports+ OR MH "Aerobic Exercises+" OR MH "Muscle Strengthening+" OR MH "Upper Extremity Exercises+" OR MH "Therapeutic Exercise") AND (MH "Arousal+" OR MH "Task Performance and Analysis" OR MH "Mental Processes+" OR MH "Neuropsychological Tests")

(MH "Cognition Disorders" OR MH "Delirium, Dementia, Amnestic, Cognitive Disorders+") AND (MH "Exercise+" OR MH "Physical Fitness+" OR MH "Sports+ OR MH "Aerobic Exercises+" OR MH "Muscle Strengthening+" OR MH "Upper Extremity Exercises+" OR MH "Therapeutic Exercise") AND (MH "Arousal+" OR MH "Task Performance and Analysis" OR MH "Mental Processes+" OR MH "Neuropsychological Tests")

AMED

((DE "COGNITION DISORDERS") OR (DE "MILD COGNITIVE IMPAIRMENT")) AND ((DE "EXERCISE") OR (DE "EXERCISE MOVEMENT TECHNIQUES") OR (DE "EXERCISE THERAPY") OR (DE "EXERCISE TESTING") OR (DE "PHYSICAL FITNESS") OR (DE "AROUSAL") OR (DE "MENTAL PROCESSES") OR (DE "TASK PERFORMANCE AND ANALYSIS") OR (DE "PERCEPTION") OR (DE "OUTCOME AND PROCESS ASSESSMENT") OR (DE "NEUROPSYCHOLOGICAL TESTS") OR (DE "MILD COGNITIVE IMPAIRMENT"))